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## PREVENTIVE MEDICINE AND THE NEW EPIDEMIOLOGY: HEART DISEASE AS A PROBLEM IN COMMUNITY HEALTH.[1]


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Creighton's great "History of Epidemics in Britain" has been largely instrumental in bringing about a return to the Hippocratic method practised by Sydenham, that of studying the natural history of disease . . . The germ theory, when it carried everything before it, in the "eighties", swept epidemiology off its feet and it was some time before the importance of *soil* (as well as of *seed*) again became fully recognized . . . It is clear that the clue to threading the mazes of epidemiology is that used by the clinician attempting to bring within his "unity of apperception" the vivid impressions passing through his mind as he scrutinizes his patient.

—Sir William Hamer,
in "Epidemiology Old and New" (1928).

Individual pathology deals with the quality and effects of diseases and, in practice, assists diagnosis and treatment; social pathology deals with quantity and causes of diseases, and, in practice, assists prevention . . . Social pathology has required the emergence and adaptation of methods of clinical, social and specialist inquiry. Its epidemiological studies are concerned with the incidence and trends of diseases in the living community or its component groups . . . With a wider collection and fuller utilization of statistical material relating to all the commoner types of disease and injury—and not merely those due to crowd infection and connected especially with childhood, insanitary conditions, and war—the horizons of epidemiology will by degrees be greatly expanded.

J. A. Ryle, in "Changing Disciplines" (1948).

### The Old Epidemiology.

NO DOUBT man has ever been concerned about his illnesses and their causes. Certainly the great epidemics have always caused him the gravest anxiety. There was a mystery about them. Whence came they? And why? It is not surprising that he should have blamed some supernatural power, some evil spirit, for attacking him, or the gods for visiting their wrath, or the stars for exerting a malign influence. Less than 200 years ago Mesmer got his doctorate in Vienna for a thesis on the influence of the planets on human health. The famous Passion Play of Oberammergau has been performed, every ten years for over 300 years, in fulfilment of a vow of the villagers in token of their being spared by supernatural intervention from the threatening plague.

The medical men of old intended their minds on the problems of epidemics. Early in the sixteenth century Fracastorius, the first epidemiologist, formulated many

[1] Based on a paper read before Section I at the meeting of the Australian and New Zealand Association for the Advancement of Science on January 23, 1957, at Dunedin.

ideas about *contagium vivum*, ideas which could be clarified and understood only after the days of Pasteur. Later, in England, Sydenham studied the geography and meteorology of epidemics, and the rhythmic periodicity of their recurrence. He attributed outbreaks of contagious diseases to cosmic atmospheric influences, or to miasms from the bowels of the earth. He based his theory of "epidemic constitutions"—better expressed as "epidemic constituents"—on the old ideas of Hippocrates.

Late in last century, August Hirsch (1883) wrote his classical work on the science of historical and geographical pathology. He defined this science, which came to be called "epidemiology", as one which "will give, firstly, a picture of diseases of mankind, in distinct epochs of time and at various places on the earth's surface, and, secondly, will render an account of the relations of these disorders to the external conditions surrounding the individual and determining his manner of life". A wide field, indeed.

### Ecology: The Seed and the Soil.

From this old epidemiology of Fracastorius and of Sydenham evolved the descriptive epidemiology set out so well in such works as those of Creighton and Hirsch. What causes epidemics? The work of Pasteur and Koch focused attention on the minute organisms associated with various diseases, and it was natural to think that the disease was due solely to the attacking germ. But there are two sides to the story—the host as well as the parasite has to be thought of. Let us remember, too, that Koch himself never claimed that the discovery of bacteria solved all the problems of herd illness (Greenwood, 1932).

Certainly, for infection to occur we postulate the presence of the germ. But the individual infected is important too. For disease to occur at least two factors are necessary—a potent germ and a susceptible host. By way of illustration, the parable of the seed and the soil has often been used, notably by Osler. In recent years, host-parasite relationships in disease have received increasing attention as studies in ecology. Burnet has clarified that aspect exceptionally well.

And epidemiology has grown. There are now many kinds of epidemiology besides the old descriptive sort. We hear of analytical, experimental, field and serological epidemiology. There are global epidemiology and micro-epidemiology and even "epidemiology in reverse". For the ordinary physician like myself it has become a complex business.

Over the past twenty years, experimental epidemiology has received its special impetus from British workers, especially Greenwood, Bradford Hill, Topley and others associated with the Medical Research Council (1936), and from Webster and his colleagues in the United States of America. Many of the problems of disease are now tackled by medical research institutes throughout the world by experimental methods. The Chairman of this Section (Professor Frank Fenner) has devoted himself to such studies; Florey, Burnet and other distinguished workers have similar interests. Topley and his colleagues reviewed the rise of epidemiology, from the descriptive kind to the experimental. They showed that the statistical method had defined the problems of epidemiology in a way that unaided description could not approach, and that bacteriological and immunological methods had scored further successes. From statistical, bacteriological and immunological considerations, they discussed in their report the features observed and the factors operating in the natural evolution of an epidemic or in endemic prevalence. They claimed for their work, which involved over 100,000 mice, little more than that they had cleared the ground for future studies. They were able to maintain herds for years without the accidental introduction of any extraneous infection, and to keep infection with various bacterial parasites active without any cross-infection. In the case of the virus infection ectromelia, their early work at least was often spoilt by the accidental transference of that virus to a herd infected with some other disease. It lies within neither my present function nor my ability to elaborate further the methods and findings of experimental epidemiology, beyond mentioning that the method has long since established its superb value in epidemiological studies. In its various aspects, epidemiology as a study of infections has won for us in the case of many diseases a clear understanding of their causes and their manner of spread, and has enabled us to introduce methods of control.

### The New Epidemiology.

Until recent years epidemiology concerned itself with germ-caused illnesses, the infectious diseases. Lately, it has become accepted practice to speak of the epidemiology of practically any common illness—non-infectious as well as infectious—and even of the "epidemiology of health" (Gordon, 1954).

The question has been raised as to the propriety of this wide use of the term "epidemiology". We speak of the epidemiology of measles, or smallpox, or typhoid fever, or tuberculosis. Is it proper to speak of the epidemiology of, say, cancer of the breast, or cirrhosis of the liver, or housemaid's knee, or ingrowing toenails? An old definition (Sydenham Society) described an epidemic disease as one "prevalent among a people or a community at a special time, or produced by some special causes not generally present in the affected community".

An epidemic is something "upon" or "among the people". The word has, of course, been used for conditions "among the people" other than illnesses. Scott spoke of the "epidemic terror of an imaginary danger". Swift referred to the "trade of universal stealing" as an epidemic, Burke wrote of an "epidemic of despair", and Brodie mentioned "epidemics of opinion" as well as of disease. Milton spoke of the "toleration of epidemic whoredom". There is no lack of precedent and authority for a wide interpretation of the word.

It is surely useful for the physician, attending victims of illnesses current in the community, to ask himself "why?"—why is this disease "among the people"? Seeking, and sometimes finding, answers to that question cannot fail to direct thought and action to prevention. Through studies so engendered, the "horizons of epidemiology will by degrees be greatly expanded" (Ryle). The wide and uniform use of epidemiological principles will surely lead to continuing triumphs in the control of disease.

"Heart Disease: Biggest Killer in Australia" was a heading in a recent newspaper; of 80,000 deaths each year, 27,500 were recorded as due to heart disease, and 11,000 to cerebral vascular accidents. Cardio-vascular diseases are certainly common: for every 100,000 people in Australia and New Zealand there are each year 900 deaths, 350 of them due to cardio-vascular diseases, 150 to cancer, 50 to violence (25 of them in road accidents), 20 to pneumonia, 15 to diabetes, 10 to tuberculosis, 10 to nephritis, and 0·1 or less to diphtheria. Whether we say it is an epidemic or not, cardio-vascular diseases weigh heavily indeed "upon the people"; their epidemiology deserves study.

### Heart Disease in the Community.

It would appear that I am establishing almost a ten-year rhythmic periodicity in presenting papers to this Section on the community aspects of heart disease. Members may fear that these inflictions of mine threaten to be a recurring outbreak. In 1937, at Auckland, I gave a presidential address on the subject (Southwood, 1937), and in 1949 at Hobart I elaborated some aspects of it. Today I would say something on the application of epidemiological principles to the study of heart disease.

Heart disease is, of course, no simple entity. It is really a bunch of diseases, a number of pathological conditions, which can be grouped for study under several headings: there are, for instance, congenital conditions, rheumatic heart disease, syphilitic heart disease, and heart disease from high blood pressure, from thyrotoxicosis (and from myxœdema as well), and from the so-called degenerative conditions in which atheroma is generally included.

The nature and the extent of the problem, especially as it appears in Australia, I shall illustrate with charts. For the most part, they are based on figures supplied by Mr.

H. L. Semmens, of the South Australian Statistical Department, through the courtesy of the Government Statist, Mr. A. W. Bowden. Several of the charts are reproduced (Figures I to VI).

In considering heart disease as a problem in public health, the main relevant points may be summarized as follows:

1. In most countries there has been a continuing and rapid increase in the proportion of deaths attributed to diseases of the circulatory system (Figures I and II). The fact that other diseases, especially the infections, cause fewer deaths now than formerly accounts for much of that increase.

2. The increase has occurred especially in the older age groups, in people aged over fifty years. It appears that middle-aged men are also being increasingly attacked.

3. The increase is especially noted in countries where the population is aging, in places where an increasing proportion of the people is living to advanced years. In most countries the advances in medical knowledge and in economic status have been accompanied by this altered population spectrum. The change in Australia is shown in Figure III.

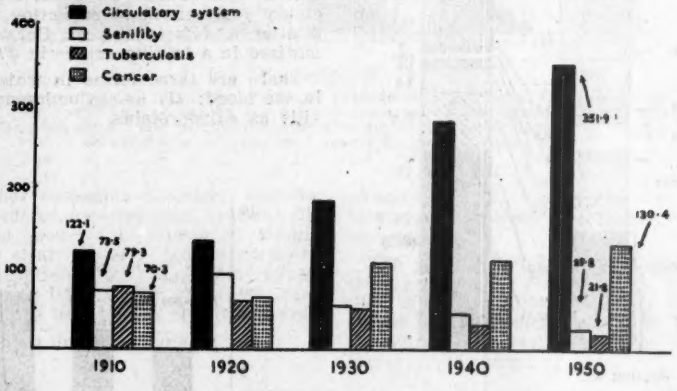


FIGURE I.

Australia: deaths from diseases of the circulatory system, senility, tuberculosis and cancer, per 1000 deaths from all causes. The chart illustrates the great increase in the proportion of deaths from diseases of the circulatory system, some increase in deaths from cancer, and the fall in deaths from tuberculosis. Over 35% of all deaths are now attributed to diseases of the circulatory system; forty years ago the percentage was just over 12.

4. Aging of the population accounts in part for the increase in deaths from circulatory diseases. In a similar way, much of the increase in the cancer death rate may be attributed to aging of the population, for cancer mainly affects people past middle life.

5. There has probably been some increase in the incidence of congenital abnormalities of the heart from recurring epidemics of German measles. The observation that German measles in the early months of pregnancy may lead to congenital malformations has been an epoch-making discovery of this century.

6. Rheumatic fever causes fewer deaths than it used to; studies in South Australia by Sangster (1940) were illuminating. Diphtheria, whooping-cough and scarlet fever are also less troublesome now than formerly (Figure IV). Since 1950, the decline in deaths from rheumatic fever in Australia has continued, and the rate in 1954 was 0·85 per 100,000 population. For some infections artificial immunization has been an active reducing agent. The use of new drugs has done wonders, especially in preventing serious death-dealing effects from infections involving the circulatory system; a striking example is subacute bacterial endocarditis, till recent years almost always fatal, but now commonly responsive to treatment. Paul White (1953) has drawn attention to the changed incidence of the several types of heart disease, especially the decline of rheumatic heart disease, and the increase of coronary diseases.

7. The increase in deaths from circulatory diseases has been due basically to arteriosclerosis, the term being used in its wide and comprehensive sense.

8. In most countries statistical returns show increase in deaths from diseases affecting the coronary arteries, the arteries of the heart wall itself (Figures V and VI). Can we call it a pandemic? It is to be borne in mind that only since 1930 has "coronary thrombosis" as a clinical entity been generally recognized, and statistics are affected accordingly.

Diseases of the coronary arteries are the outstanding cause of deaths from circulatory disorders at the present time. So great is the problem that it has attracted the attention of statesmen and of epidemiologists everywhere. What is causing the increase, and what can we do about it? The first question is for the epidemiologist; the statesman and the public health specialist are eager for help in finding answers to the second.

But first a few words about terminology. Boyd (1945) has aptly said that of all arterial lesions, arteriosclerosis is the most common, the most important and the most obscure:

> Not only is the cause unknown but the very nature of the condition is undecided, by some being regarded as inflammatory, as indicated by Virchow's term *endarteritis deformans*, by others as a degeneration. One reason why a perusal of the discussions in the literature is so confusing is that many different lesions are included under the one name of arteriosclerosis, so that now one, now another condition is being alluded to. Many writers use the term as synonymous with atheroma. This is quite justifiable as long as the reader is familiar with this usage.

The general condition of arteriosclerosis or hardening of the arteries is commonly considered as three distinct entities with distinct pathology: (i) Atheroma, with the intimal plaque as its essential lesion. In small vessels, such as the coronary arteries and the arteries at the base of the brain, this may almost wholly occlude the lumen. (ii) Mönckeberg's sclerosis, with the "pipe-stem" radial arteries, and the prominent and tortuous arteries on the temples. This is not atheroma, nor is it a lesion of the intima—it is degeneration, even to calcification, of the middle coat of the vessel. (iii) Diffuse arteriolar sclerosis especially in the small arterial branches in some viscera, notably the spleen, pancreas, kidneys and adrenal glands, in vessels of 100$\mu$ in diameter or less (Boyd). High blood pressure is often associated and probably a main cause, accentuating and speeding up the degenerative wear-and-tear process.

## Nature of Atherosclerosis.

It is not surprising that all over the world there should be a furore of interest in arterial diseases. In spite of the tremendous amount of work that has been done and is continuing, precise causes are still not wholly agreed upon by the experts. The discussion here will be brief and general. It is restricted to atheroma, for that is the circulatory disorder causing most of the trouble. The features can be touched on only lightly, for the possibilities and uncertainties are many and varied. Decisions on some aspects await the results of probably long years of painstaking investigations.

Boyd describes as follows the changes in the lesions of atherosclerosis:

> The atheromatous softening which is so characteristic of the lesion may involve the overlying thickened intima, and when the surface is reached the material is discharged into the lumen of the vessel and the atheromatous ulcer is formed. On the resulting roughened surface thrombosis may occur, and such a thrombus may form the starting point of a future embolus. The

deposition of lime salts in the fatty material may convert the lesion into a calcified plaque, with the brittleness of a shell.

Pathologists agree about the structure of the lesions found in atherosclerosis in its various stages; essentially the characters are two—a fatty change, and fibrous thickening of the intima. Argument comes when we consider how the changes arise. In recent years Duguid (1954) of Glasgow has revised the "encrustation theory" put forward by Rokitansky in 1852. The view more commonly held, however, is that the fatty materials accumulate in the connective tissue of the intima because the tissues imbibe them from the blood plasma. Such deposition of lipids is thought to occur most readily when they are present in the blood in large amounts or as unstable complexes from which precipitates easily occur (Florey, 1955). Florey has said that both imbibition and thrombosis (encrustation) "may play parts in forming the lesions of human atheroma. . . . While the imbibition hypothesis

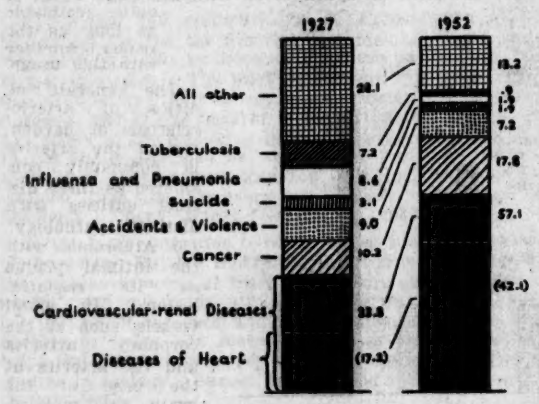


FIGURE II.

Chart prepared from figures supplied by all companies reporting to the Life Insurance Association of America. It shows the percentage distribution of death claim payments by cause of death. (From *Minnesota Medicine*, November, 1955.)

directs attention to the factors controlling the stability in solution and the distribution of the plasma lipids, the formation of small mural thrombi may be associated with a relationship of plasma lipids to blood coagulation".

It is now generally agreed that atherosclerosis is not simply a wearing-out process, the inevitable accompaniment of advancing years. There are multiple causative factors, and several of them give opportunities for prevention. Here are some factors:

### *Heredity.*

Osler attached great importance to heredity, especially when he found whole families with the tendency to early arteriosclerosis: "In the make-up of the machine bad material was used for the tubing." But Osler went on: "More commonly the arterio-sclerosis results from the bad use of good tubing." Body build may be a factor and a sort of forewarning indicator. The mesomorph (of W. H. Sheldon's somatotypes)—the stocky, thick-set person—seems especially susceptible. That is one factor we can do nothing about.

### *Aging.*

The old view that atherosclerosis was due solely to aging has been generally discarded. We do not now accept the inevitability of atherosclerosis. Besides, our main concern is atheroma in middle life, and its devastating effects.

### *The Rising Tempo of Life, with its Emotional Stresses.*

Some people are more vulnerable than others, and stand the hurly-burly of life poorly. It has been stated that "patients with coronary atherosclerosis represent a specific type of character development, and that they mask anxiety by transforming it into aggression and become active and competitive—the emotional element precipitating cardiac infarction" (Arlow, 1945).

### *Habits of Life.*

Habits of life have been "suspect". The habitual drinking of alcohol and smoking of tobacco, unless the indulgence is heavy, probably play a minor role only. Indeed, it has been shown that heavy drinking may be associated with a low serum cholesterol level and lowered incidence of atherosclerosis.

### *Exertion.*

To what extent and in what direction physical activity is relevant is a matter still to be decided; the studies of J. N. Morris (1955) indicate that physically active workers are less prone to coronary artery disease than are sedentary workers.

### *Disordered Metabolism of Fats.*

Most of the recent experimental studies have been made in the field of disordered fat metabolism. Over the last eighty years much investigation has been made into the relation of fats to disease. Current views are aptly summarized in a leading article in *The Lancet* (1956*a*).

There are three forms in which lipids are transported in the blood: (i) as chylomicrons; (ii) as $\beta$-lipoproteins; (iii) as $\alpha$-lipoproteins.

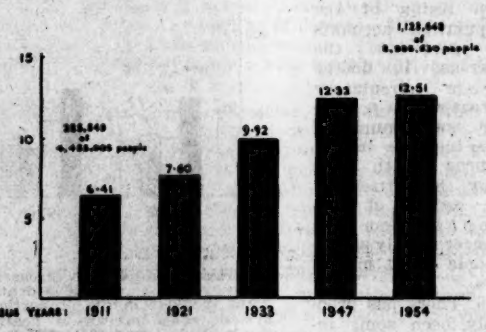


FIGURE III.

Australia: percentage of population aged over sixty years. The increasing proportion of elderly people in the community, as shown for Australia, is a common circumstance in many countries. Of a population of 9,000,000, those aged over sixty years number 1,250,000 (12·5%). It is reasonable to expect a corresponding increase in diseases of the elderly; hence the modern rise of geriatrics.

The $\beta$-lipoproteins appear closely concerned in atherosclerosis; they contain about 25% of protein, with varying amounts of cholesterol and phospholipid. As a group, patients stricken with myocardial infarction have high levels of $\beta$-lipoproteins and of cholesterol in the blood.

The work of Bronte-Stewart and his colleagues (1956) is important in showing that any dietary factor that raises the level of $\beta$-lipoprotein will also increase the liability to myocardial infarction. They found that heavy ingestion of beef dripping, butter and eggs was followed by rises in $\beta$-lipoprotein levels in the plasma; olive oil, arachis oil, seal oil and pilchard oil gave low $\beta$-lipoprotein levels. Food fats and oils are likely to influence the development of atherosclerosis according to whether or not they raise the $\beta$-lipoprotein level. Some workers have held that atherosclerosis is basically a disorder of lipid-cholesterol-lipoprotein metabolism. It has been reported that severe atherosclerosis is ten times commoner in fat people than in thin (Wilens, 1947).

More could be said on the dietary aspects and on cholesterol metabolism. What part heparin may play has also been studied by many workers. Much, indeed, remains to be clarified. For present purposes it suffices to say that

most dietary excesses—but especially an excessive intake of animal fats—favour the development of atherosclerosis. Overweight persons are certainly more likely to show atherosclerosis than their slim fellows.

### *Sex.*

Deaths from diseases of the coronary arteries occur mainly in males (Figure VI), and increasing numbers of such deaths are occurring in middle life. An interesting point is that up to middle life males show high levels of β-lipoproteins—about twice the average level found in women. In later life the difference is not observed; the level in old women is raised to that in men. Hormonal influences may be related to the different incidence of atherosclerosis in the sexes.

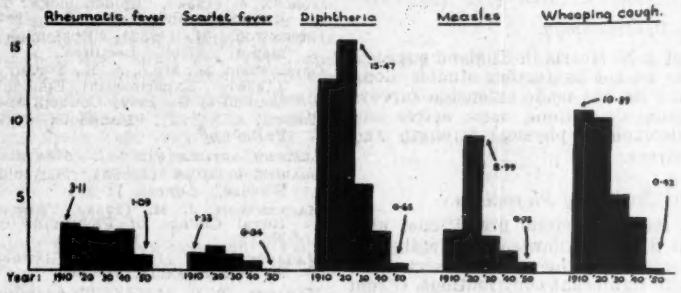


FIGURE IV.

Australia: death rates per 100,000 of population. In Australia, and in many other countries, the fall in the death rates from the common infections has been striking. The figures for Australia since 1950 show continuing decline in all five conditions, and especially in rheumatic fever.

### *Other Illnesses.*

Other illnesses, including especially hyperpiesia, diabetes, other endocrine disorders, and the neuroses, have been considered as ætiological factors. To what extent raised blood pressure is related to atherosclerosis is not entirely clear. Fairly normal coronary arteries may exist in association with long-standing hypertension. Magarey (1956) inclines to the hypothesis that atheroma is a result of wear and tear of the vessel wall,

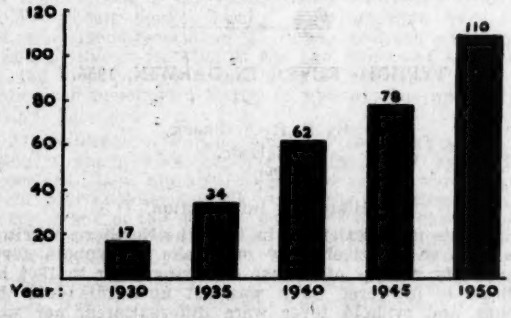


FIGURE V.

Australia: death rate per 100,000 of population from diseases of coronary arteries, including *angina pectoris*. The rapid increase in deaths from diseases of the coronary arteries is almost a world-wide feature.

and that hypertension acts by accentuating those mechanisms. Yet it appears the case that most patients with clinical coronary disease show no hypertension.

Diabetes has long been accepted as one factor in causation; the associated disturbance of fat metabolism and the common occurrence of high levels of cholesterol are suggestive features.

Disorders of the thyroid gland may also be concerned; in myxœdema subjects the concentration of cholesterol in the blood is generally high. The heavy administration of thyroid extract in normal subjects has been shown to reduce the blood level of cholesterol and of β-lipoproteins, but the associated increase in general metabolism may be dangerous through increasing the coronary load. The cholesterol-depressing effects may be increased by using the acetic-acid analogue of thyroxin ("Tetrac") or the acetic-acid analogue of tri-iodothyronine ("Triac"), and those new compounds show promise of being able to lower the blood cholesterol level without causing unwanted side effects (*Lancet*, 1956b).

### *Comment.*

In dealing with atherosclerosis, the physiologists, biochemists and pathologists have a horde of involved problems. The report of the recent Conference on Epidemiology of Atherosclerosis and Hypertension (1956), sponsored by the American Heart Association and the National Health Institute, is a stimulating record. The research goes on; the real nature of atheroma and its causes may some day become clear.

## What Can be Done?

The preceding section has presented but a cursory review of current ideas of the nature and causes of atherosclerosis; it is enough to show that action to prevent the damage done by the disorder is not clearly definable. Can anything at all worth while be done to stay the increase of the heavy losses our communities are suffering?

The preventive medicine for ills at any stage in life is largely a matter for attention in the preceding stages. Care of infants promotes healthy childhood, and the health of the adult depends largely on the care given to it by himself and others in youth and childhood. The child is father of the man.

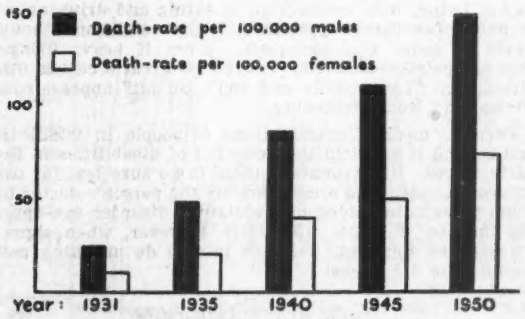


FIGURE VI.

Australia: deaths from diseases of coronary arteries including *angina pectoris*. The increase in deaths from diseases of the coronary arteries is shown for both sexes; the incidence in men continues to be about twice that in women.

The sudden *exitus* of too many men in active middle life, from coronary artery disease or any other cause, is a distressing fact; it is the main warrant for community concern and action. The effects of atherosclerosis in old people we accept almost complacently. But should we?

The prime need is for continued research. Epidemiology applied to atherosclerosis is a fairly new business, and many questions await answer. The experimental approach, mainly with the use of animals in laboratories, is likely to give help. Care has to be taken, of course, in applying the results of animal experiments to problems affecting human subjects. Magarey (1955) has pointed out "the unwisdom of drawing too close an analogy between the lesions

induced in rabbits and the human disease". Much remains to be done in metabolic studies, in carnivores and in men. What may be termed the ecology of coronary artery disease provides an ample field.

The following is a brief summary of lines of endeavour.

### *Continued Research.*

Research, mainly in experimental epidemiology, is throwing some light on the pathogenesis of atherosclerosis.

### *Field Epidemiology.*

The well-known work of J. N. Morris in England suggests that results of value may be got by further studies along the lines he has followed. He has made extensive surveys of men exposed in various occupations, some active and some sedentary, some demanding physical strength and some providing mental stress.

### *Observations of Practising Physicians.*

The general physician and the general practitioner may do much. Even without detailed knowledge of pathology and experimental epidemiology, the keen observer in medical practice may make significant contributions. From carefully kept records, covering long years of observations of the health of people of a fairly fixed community, deductions of high value may come. The newly fledged College of General Practitioners may find here an opportunity for effort and for gaining laurels. Mackintosh (1954), in his John Matheson Shaw Lecture, gave a rousing call for research in general practice. The opportunity is there.

### *The Potential Sufferers.*

While all the studies are going on—and there seem years of work ahead—what can people do to protect themselves against atherosclerosis and its dire effects? This is an age of medicaments—tablets for this and elixirs for that—but against atherosclerosis there is so far little hope of help from special medicaments or "wonder drugs". In the present state of knowledge—or the lack of it—it can be said that the only helpful plan is to adopt a steady, orderly way of living, with moderation in eating and drinking, and to avoid (as far as practicable) the conditions thought likely to cause atherosclerosis. Even if heavy drinkers may escape atherosclerosis, it is at too great a cost in other directions. "Live calmly and don't get fat" appears sound advice, and worth following.

Periodic medical examinations of people in middle life and beyond it assist in the detection of disabilities in their early stages. Unfortunately, there is no sure test for early atherosclerosis. The recognition by the person's doctor that some threatening signs of circulatory disorder are appearing may be of value. Generally, however, when signs of disease are apparent, it is too late to do anything really useful—the die is cast.

### *Public Health Authorities.*

Recent years have seen many changes in the range and nature of the tasks undertaken by boards of health and similar bodies. The term "human ecology" has come into use, and "epidemiology" now means more than the study of germ-caused outbreaks of illness. There has been a shift to the personal. Social aspects of living, rather than environmental affairs and sanitary engineering, have become a prime concern of public health.

Epidemiology in the study of infections has often enabled effective control to be adopted. The wider use of the epidemiological method, the study of non-infectious diseases occurring in groups of people, may confidently be expected to aid in solving their problems. The ill effects of atherosclerosis, especially the loss of many men in their vigorous years, may eventually be countered by the untiring application of the principles of the new epidemiology.

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## TYPHOID FEVER IN DARWIN, 1955.


By R. R. A. BROCK,
*Adelaide.*


### Historical Introduction.

SINCE its first settlement in 1824, the Northern Territory has suffered relatively few outbreaks of typhoid fever. The scanty records of disease occurring prior to 1869 are difficult to interpret, as it was not until this date that typhus and typhoid fever were differentiated, nor were any accurate estimates made of disease incidence or causes of death. Diagnoses were probably often those of lay persons. Thus Major Campbell, as quoted by Cumpston and McCallum (1927), in a memoir describing the diseases prevalent at the settlement on Melville Island in 1824, enumerated "intermittent, acute, and typhus fever . . . dysentery, diarrhœa, rheumatism, scurvy, and nectatopia; the latter disease very common".

Cook (personal communication, 1956) stated that "typhoid was fairly regularly reported during the South Australian administration in the 80's and 90's". The Government Resident's report on the Northern Territory for 1894 contains the first available statistical record of typhoid fever, one case being recorded. The Government Resident was notified of no further case until 1911, when the only recorded death from typhoid fever in the Northern Territory occurred. In 1912 there was an outbreak of the disease at Batchelor's Farm, 21 miles from Darwin. The Chief Medical Officer reported to the Administrator that workmen were living in tents and that the camp hygiene was bad. Five of them were infected by a carrier. During 1913 three further patients with typhoid fever were treated in Darwin Hospital.

Since that time the only infectious gastro-intestinal diseases reported have been bacillary and amœbic dysentery, non-specific gastro-enteritis, infantile diarrhœa, paratyphoid B fever, and ancylostomiasis, all except the last being in small numbers. The paratyphoid B cases occurred in an aboriginal and a white civilian at Katherine in 1943. Shortly afterwards three soldiers at 121st Army General Hospital contracted the same illness (Walker, 1952).

### The Present Investigation.

This report describes the epidemiology, bacteriology and clinical aspects of a small outbreak of typhoid fever in Darwin which occurred between March 11, 1955, and August 16, 1955, and which affected one carrier and five other patients. The Northern Territory Director of Health, Dr. A. H. Humphry, supervised the health survey described below. The bacteriological tests were carried out by the pathologist of the Darwin Health Laboratory, Dr. T. A. Nowell. The role of the writer was that of clinician.

### *Epidemiology.*

On March 11, 1955, a child from Parap Community Camp developed typhoid fever. This was diagnosed at Darwin Hospital on March 25, 1955.

Parap Community Camp is a legacy of the 1939-1945 war and is adjacent to the Stuart Highway, being two miles from Darwin Post Office. It comprises nine acres of "Sydney Williams" huts. The widest diameter of the area is 700 feet. Sewering had been commenced two and a half years prior to the outbreak of typhoid fever, but had not been completed. In 19 homes incinerator latrines were in use, many in poor repair. Most of the population of approximately 300 were part-aboriginal with a low standard of hygiene.

No evidence of fæcal contamination or of *Salmonella typhi* was found in monthly bacteriological cultures of the Darwin water supply or in a water sample taken from a tap in the first patient's home on March 25. The majority of those living in the Parap Camp ate tinned foods and cooked meats bought locally. Few attempts were made to protect food from flies. There was no fresh milk supply. Those living or working at the two shops and the bakery in the locality were tested by three successive fæcal cultures, commencing on March 26, and in none was *S. typhi* found.

All residents of Parap Camp and 100 other school and social contacts were bacteriologically tested by methods described below. On April 10, positive results were obtained from two adolescent girls. One was suffering from an acute attack of the disease, while the other was symptomless and afebrile. Both had arrived in Darwin from Broome six weeks earlier.

The Western Australian Commissioner for Public Health, Dr. L. Henzell, in a personal communication, states that no cases of typhoid fever were reported from the northern portion of Western Australia during 1955.

Subsequently three more residents from the neighbourhood of Parap Camp contracted the illness, on May 9, on August 15, and on August 16. Ten household contacts were found to have significant amounts of Vi agglutinins suggestive of a carrier state (Felix, 1938); but stool cultures produced no growth of *S. typhi*. No further cases of typhoid fever have been diagnosed in Darwin in the subsequent year (A. H. Humphry, personal communication, 1956).

### *Bacteriological Investigations.*

The preliminary health survey, which commenced on March 25, included the collection of fæcal specimens from 221 adults and 179 children in the vicinity of the home of the first typhoid fever patient. Single specimens (without previous purging of the contacts) were inoculated into tetrathionate broth and sub-cultured twenty-four hours later on to bismuth sulphite agar. Typical colonies were picked off and tested after twenty-four hours and forty-eight hours incubation. By this method one carrier and one subject with an acute case were detected.

In the search for a further carrier the method followed was that recommended by McCartney as given by Mackie and McCartney (1950). Sera of the suspects were tested for Vi agglutinins, first with the use of the Vi form of *S. ballerup* and later with the Vi strain of *S. typhi* Vi 1. The former gave positive results at considerably higher titres than the latter. Dr. Nancy Atkinson, Reader in Charge of Bacteriology, University of Adelaide, who performed the majority of Vi agglutinin serological tests, advised that titres less than 1/80 with *S. ballerup* Vi and less than 1/20 with *S. typhi* Vi 1 were probably of no significance. Of 28 home contacts tested, eight were found to have Vi agglutinins at titres exceeding these values. Each contact was given two grains of calomel followed by a saline purge, and selenite F medium was inoculated from the third stool evacuated. The enrichment medium was later subcultured on desoxycholate-citrate agar.

TABLE I.
*Temperature-Pulse Ratios in Adult Cases of Typhoid.*

| Temperature. (Degrees Fahrenheit.) | Average of All Pulse Rates (per Minute). | |
|---|---|---|
| | During First Three Weeks. | During Next Six Weeks. |
| 97 | 90 | 88 |
| 98 | 68 | 72 |
| 99 | 90 | 103 |
| 100 | 95 | 102 |
| 101 | 102 | 107 |
| 102 | 103 | 121 |
| 103 | 108 | 121 |
| 104 | 109 | 125 |
| 105 | 110 | — |

The organisms from each typhoid patient were sent to the Public Health and Bacteriological Laboratories of the University of Melbourne for the identification and phage typing. They were found to be the most common type in Australia (E1).

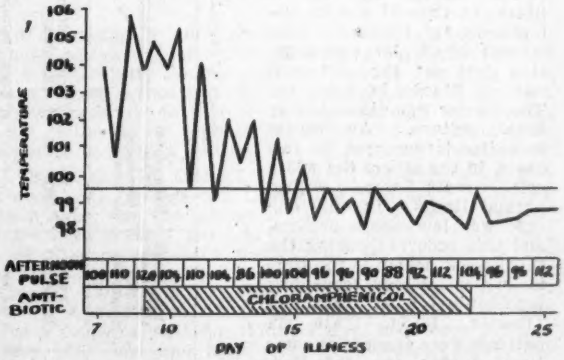


FIGURE I.
Case II: Temperature, pulse and treatment chart.

In the four cases diagnosed in Darwin Hospital, the organisms were tested for sensitivity to penicillin, streptomycin, chloramphenicol and oxytetracycline by the method of placing paper disks containing the antibiotics on an inoculated culture medium.

Sensitivity to chloramphenicol was either equal to or greater than sensitivity to oxytetracycline, the only exception being the culture in Case IV. Here the organisms were sensitive to oxytetracycline and streptomycin but insensitive to chloramphenicol. Streptomycin had a pronounced in-vitro action, but did not affect the course of the disease in this case (Table II and Figure II).

*Clinical Features.*

A summary of the clinical features is given in Table II. All six patients were either part-aboriginal, or part-Asiatic, or both. Generally speaking the illness was not severe. Of the six cases diagnosed, in five there were signs of overt disease, while the carrier was free of symptoms. The patients with acute infections suffered with remittent fever and lassitude; there was a delirium typical of typhoid in two instances. The pulse-temperature ratio was depressed at temperatures above 101° F. during the first three weeks (Table I, Figures I and II).

Three patients had bronchitis with the onset of their symptoms, two had initial diarrhœa, two were disturbed by vomiting, and one was constipated. Some abdominal distension occurred in all the acute cases. This was particularly pronounced in the two children in the series, who displayed a typical "doughiness" on palpation. In two cases the spleen was enlarged and tender. Rose spots were not detected on any of those affected.

The diagnosis was established by blood culture on the third day of illness in Case V and on the tenth day of illness in Case VI, by fæcal culture on the fifth day of illness in Case II and on the tenth day of illness in Case I, and by Widal agglutination test on the sixteenth day of illness in Case IV. The carrier was diagnosed by fæcal culture. An initial leucocytosis occurred in two cases, in the others the white cell counts were within normal limits. In only one case was leucopenia present, and this occurred during the third week, which is the time at which Beeson considers leucopenia most common (Beeson, 1955). All six patients were anæmic at some time during the infection, their hæmoglobin values ranging from 8·7 to 12 grammes per 100 millilitres. This could not be attributed in all cases to typhoid, as three of the women were pregnant and one had recently given birth to an infant, and these women had been eating inadequate diets. They were all found to be free from ancylostomiasis. The patient in Case II was twenty-two weeks pregnant and the patient in Case III was fourteen weeks pregnant

TABLE II.

*Summary of Clinical Features, Six Cases of Typhoid Fever, 1955.*

| Case Number, Patient and Age (Years). | Clinical Features. | White Blood Cells (per Cubic Millimetre). | Hæmoglobin Value. (Grammes per Centum.) | Bacteriological Findings. | Antibiotics to which *Salmonella typhi* was Sensitive. | Therapy. (Milligrammes per Kilogram per Day.) | Duration of Therapy. (Days.) | Results. |
|---|---|---|---|---|---|---|---|---|
| I, boy, 4. | March 11, developed lethargy, anorexia, intermittent vomiting, diarrhœa, wasting, fever and abdominal distension. April 18, relapsed, with lethargy, fever and abdominal distension. | 11,000 (March 21)<br>12,300 (April 28) | 10·5 (May 11)<br>— | Fæcal culture: *S. typhi* (March 21).<br>Fæcal culture: *S. typhi* (April 18). | Chloramphenicol (March 21).<br>Chloramphenicol, oxytetracycline, streptomycin April 18). | Chloramphenicol, 63 (March 25).<br>Chloramphenicol, 63 (April 18); tetracycline, 25 (May 11). | 14<br>10<br>12 | Fever resolved in 14 days; fæces "negative" in 10 days.<br>Fever resolved in 10 days; fæces remained "positive"; Fæces "negative" thereafter. |
| II, Domestic, 18. | April 3, developed malaise, constipation, fever; 22 weeks pregnant. | — | — | Fæcal culture: *S. typhi* (April 8). | — | Chloramphenicol, 61 (April 12). | 13 | Fever resolved in 7 days; fæces "negative" thereafter. |
| III, Domestic, 15. | No symptoms. Health survey stool culture (April 8) produced *S. typhi*; 14 weeks pregnant. | 14,700 (April 22). | 10·9 (May 3). | Fæcal culture: *S. typhi* (April 8). | — | Chloramphenicol, 59 (April 22). | 11 | No fever throughout; fæces "negative" thereafter. |
| IV, Housewife, 24. | May 9, developed weakness, intermittent diarrhœa, rigors (two weeks), fever; lactating, 9 weeks pregnant.<br>June 10, relapsed, with malaise, vomiting, fever.<br>July 21, aborted spontaneously. | 4500 (May 24)<br>—<br>10·8 (June 21) | — | Serum agglutinated *S. typhi* O, 1 : 160. No agglutination to *S. typhi* H, *S. paratyphi* A, B and C (May 25).<br>Fæcal culture: *S. typhi* (May 25).<br>Fæcal culture: *S. typhi* (June 7). | — | Chloramphenicol, 52 (May 28).<br>Streptomycin, 42 (June 17).<br>Tetracycline, 52 (June 21). | 11<br>4<br>18 | Fever resolved in 6 days; fæces remained "positive".<br>Fever persisted.<br>Fever resolved in 16 days; fæces "negative" thereafter. |
| V, Housewife, 23. | August 16, developed headache, backache, paræsthesiæ of fingers, nausea, cough, tender spleen; lactating. September 7, relapsed, with malaise and fever. | 6000 (August 19)<br>—<br>12·0 (September 12) | — | Blood culture: *S. typhi* (August 19).<br>Fæcal culture: *S. typhi* (August 19).<br>Fæcal culture: *S. typhi* (September 12). | Chloramphenicol and oxytetracycline in that order (August 19).<br>— | Chloramphenicol, 43 (August 22).<br>Oxytetracycline, 54 (September 16). | 14<br>13 | Fever resolved in 7 days; fæces temporarily "negative".<br>Fever resolved in 5 days; fæces "negative" thereafter. |
| VI, Boy, 7. | August 15, developed headache, vomiting, abdominal pain, cough, fever, rhonchi in chest, splenomegaly. | 6100 (August 26) | 10·8 (September 1) | Blood culture: *S. typhi* (August 25). | Sensitive to chloramphenicol, slightly sensitive to streptomycin, resistant to oxytetracycline (August 25). | Chloramphenicol, 62 (August 21). | 13 | Fever resolved in 15 days; fæces "negative" thereafter. |

when typhoid was detected, but neither patient was affected by the infection.

The only complication arose in Case IV, in which abortion occurred at about the eighteenth week of pregnancy.

*Treatment.*

The patients were admitted to hospital and retained until three consecutive stools at forty-eight-hour intervals were found on culture to be free from *S. typhi*. The duration of therapy varied from thirty-three days in Cases II and III to 104 days in Case I. The prolonged stay in Cases I, IV and V was due to the disease being resistant to chloramphenicol.

Affected patients were put to bed in isolation and given a light diet. Table II shows the antibiotics used. In all but the last case treatment commenced with chloramphenicol in a dosage of 43 to 63 milligrammes per kilogram of body weight per day (2·5 to 3·0 grammes per day for an adult). The carrier (Case III) was cleared by an eleven-day course of chloramphenicol in a dosage of 59 milligrammes per kilogram per day. The patients in Cases II and VI were cured by thirteen-day courses of this drug in doses of 61 to 63 milligrammes per kilogram per day.

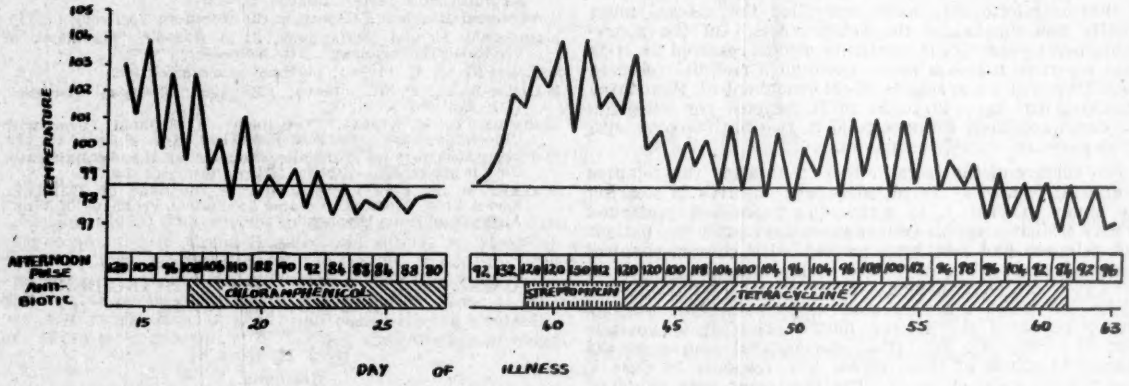


FIGURE II.
Case IV: Temperature, pulse and treatment chart.

Only in Case IV did in-vitro tests indicate resistance of the organisms to this drug. In Cases I and IV it was impossible to clear the fæces of *S. typhi* by the use of chloramphenicol in doses of 63 and 52 milligrammes per kilogram per day respectively. One patient (Case I) relapsed on the tenth day after ceasing this treatment, and another (Case IV) on the eleventh day; a third patient (Case V) relapsed two days after cessation of chloramphenicol therapy. Sensitivity tests in these cases indicated oxytetracycline as the drug of first or second choice. This was effective in a dosage of 54 milligrammes per kilogram per day in Case V. Two patients (Cases I and IV) were treated with tetracycline in dosages of 25 and 52 milligrammes per kilogram per day respectively.

During November, 1955, all previously infected persons were reviewed and subjected to the McCartney method of fæcal culture (Mackie and McCartney, 1950) without any evidence of persistence of the carrier state.

*Preventive Measures.*

Infected persons were treated in isolation in Darwin Hospital. Excreta and articles used by them were disinfected. Contacts living in the same houses as the patients were quarantined until culture of the fæces gave negative results. When the last two cases were diagnosed in August, 1955, bacteriological screening of contacts was extended from fæcal cultures on three consecutive days to post-purgation fæcal cultures of those having Vi agglutinins in significant titres. Susceptible persons were not immunized by T.A.B. inoculation for the following reasons: (i) The outbreak appeared small. (ii) Inoculation with typhoid vaccine might have complicated the epidemiological problem by increasing Vi agglutinin titres (Manson-Bahr, 1950). (iii) Such a campaign could not be made compulsory. Previous experience with inoculations indicated that the public response of Parap Camp residents would be poor.

Fly-proof pan latrines were substituted for defective incinerator latrines, and steps were taken to complete the sewering of Parap Community Camp. The public were advised individually and through the Press and radio of the precautions necessary to prevent infection.

## Discussion.

*Epidemiology.*

The 1939-1945 war solved one of Darwin's hygiene problems but created another. Chinatown was an insanitary slum area. The local authorities' efforts to clean up the place were eclipsed by Japanese bombing, and these slums did not reappear after the war. However, what is now known as Parap Community Camp came into existence, and it presents many similar sanitary problems, such as overcrowding of substandard dwellings and incomplete sewering of the area. It is scarcely to be wondered at that the only outbreak of typhoid fever in Darwin since 1913 occurred in such a locality.

The patients in Cases I, II and III lived in unsewered homes with fly-infested incinerator latrines. It seems most likely that the patient in Case III, who was a carrier, introduced typhoid fever to Parap Community Camp, and that flies subsequently transmitted the disease to the patients in Cases I and II. The mode of infection in Cases V and VI is not clear. These patients became ill on about August 15, 1955. The patient in Case IV, who was a frequent visitor to Parap Camp, may have infected them after she had been treated. However, subsequent cultures of her fæces produced no growth of *S. typhi*.

The success of the public health measures adopted can be gauged by the small number of acute cases which occurred. The Vi agglutination tests indicate that there were a number of subclinical infections. However, the outbreak became predominantly an exercise in preventive medicine rather than an epidemic of any great clinical magnitude.

*Clinical Findings.*

The failure to note rose spots on any patient was somewhat unusual, even in this small series. Manson-Bahr (1950) considers them one of the five diagnostic criteria. They were seen on 50% of the 300 patients treated by Marmion (1952). The fact that four of the present group were part-aboriginal and two were part-Asiatic should not have precluded the observation of rose spots, since the

erythema of such conditions as tinea and active leprides can be distinguished in the skin of such people. Beeson (1955) comments that the typhoid rash is difficult to distinguish in the Negro.

*Bacteriology.*

The same organisms (*S. typhi* type E1) were isolated from each case. There was some variation in sensitivity to antibiotics (Table II), but such variations are known to occur (McCartney, 1956).

*Therapy.*

A relatively low dosage of chloramphenicol, as recommended by Beeson (1955), was used in all cases, in order to avoid the toxic symptoms which accompany the higher dosage often used in treating typhoid fever. No side effects such as vomiting, diarrhœa or stomatitis occurred. However, a dosage of from 43 to 63 milligrammes per kilogram per day was not curative in three cases, despite in-vitro test results indicating sensitivity of the bacteria to chloramphenicol in two of these. A large initial dose of this antibiotic may have controlled the disease more rapidly and minimized the relapse rate. On the above-mentioned treatments the patients' fevers resolved by lysis after seven to fourteen days. Marmion's patients received initial doses of 3·5 grammes of chloramphenicol, then three grammes per day (40 to 50 milligrammes per kilogram per day), and their fevers settled in two to five days, with a relapse rate of 28% (Marmion, 1952).

The efficacy of the tetracyclines in treating the relapses is difficult to assess. Tetracycline was effective in clearing the stools in Case I, in which the fæces had continued to give positive results twenty-three days after the patient had relapsed and had been treated with chloramphenicol a second time. Five days after relapsing, the patient in Case IV was given an eighteen-day course of tetracycline. Figure II shows the very slow response to this therapy (fever persisted for sixteen days). Thus it is possible that the drug did not affect the natural course of the disease in either of these cases. The response in Case V was a little more clear-cut. The treatment with oxytetracycline commenced eight days after relapse; the patient was symptomless five days later, and fæces remained free of Salmonella organisms thereafter.

In the experience of others, eradication of the carrier state remains a problem. Thus Beeson (1955) considers chloramphenicol ineffective. Marmion (1952) rendered two fæcal carriers free from Salmonella organisms with this drug. The carrier in the present series remained free from Salmonella organisms according to the results of four fæcal cultures in the seven months subsequent to treatment with chloramphenicol.

## Summary.

1. During 1955 an outbreak of six cases of typhoid fever occurred in Darwin, forty-two years after it had last been detected in the Northern Territory.

2. Those affected lived in or near an unsewered section of Parap Community Camp. The second patient found was a carrier. It is thought that she was the source of the infection, which was at first spread by flies.

3. *S. typhi* type E1 was isolated from each patient. The organisms tended to be most sensitive to chloramphenicol *in vitro*, but in one case were insensitive to this drug though sensitive to oxytetracycline.

4. Rose spots were not seen on any patient.

5. In three patients the infection was controlled by chloramphenicol; three others relapsed after initial improvement on this drug. Two of the latter recovered whilst having tetracycline therapy, and the third responded to oxytetracycline.

## Acknowledgements.

The Northern Territory Director of Health, Dr. A. H. Humphry, supervised the health survey carried out by Mr. L. M. Tivendale and Mr. G. W. McComish, health inspectors; the bacteriological tests were carried out by the Darwin pathologist, Dr. T. A. Nowell; Dr. Nancy Atkinson, Reader in Charge of Bacteriology, University of Adelaide, performed the majority of the Vi agglutination tests; and Dr. J. E. McCartney, of the Institute of Medical and Veterinary Science, Adelaide, assisted with advice on culture methods. Dr. T. O. R. Yates, Medical Superintendent of the Darwin Hospital, assisted in research into hospital records. Dr. C. E. Cook furnished historical data. Both he and Dr. R. V. Southcott have offered useful criticism and encouragement. I am grateful to all these persons for their help, and wish to thank the Commonwealth Director-General of Health, Dr. A. J. Metcalfe, for permission to publish this paper.

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# COARCTATION OF THE AORTA: ITS INCIDENCE AND X-RAY DIAGNOSIS.[1]

By J. H. HOOD,
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BY coarctation of the aorta is meant a congenital narrowing or complete obstruction of a segment of the aorta. Classically, this occurs at a site just distal to the origin of the left subclavian artery in the region of the insertion of the ligamentum or *ductus arteriosus*. In very rare instances the abnormality is found at other sites in the thoracic and abdominal portions of the aorta, but I have not encountered such a case.

The effect of the constriction, particularly if it is a narrow or complete one, is to increase the blood flow and pressure in all the vessels proximal to it and to decrease the flow and pressure in all the vessels distal to it. The actual mechanism by which the blood pressure becomes elevated is still controversial, and it is not proposed to discuss this aspect of the condition. In the typical case, therefore, the patient is found to have hypertension in the upper limbs and an absence or diminution of the femoral pulses. It does not appear to be generally known that the femoral pulses may be palpable, and I have encountered several cases in which the diagnosis of coarctation had been considered but dismissed, because pulsation in the femoral arteries was detected. Not all patients present with the typical clinical features, and it is in these that a knowledge of the radiographic appearances is important. Familiarity with these appearances will also result in the detection of a greater number of cases on the routine examination of chest films.

## Incidence.

It is always difficult to determine the incidence of a congenital disease in the community, and at the best such a figure is usually only a rough estimate of the true state of affairs. Coarctation of the aorta may exist in all grades of severity, varying from a slight and insignificant narrowing of the aortic lumen to a complete obstructive

[1] Read at a meeting of the College of Radiologists of Australasia, Melbourne, November, 1954.

lesion accompanied by severe hypertension (Figure II). In addition, the more severe forms may be associated with a variety of other congenital abnormalities terminating life in early infancy. Fortunately, the radiological appearances of the chest in adults are frequently diagnostic, so that in chest surveys we have a means of estimating the frequency with which we may expect to see this condition in our own practice. However, the acceptance of any such figure as being accurate presupposes that the X-ray features are generally known—a fact which I rather doubt and which has prompted the writing of this article.

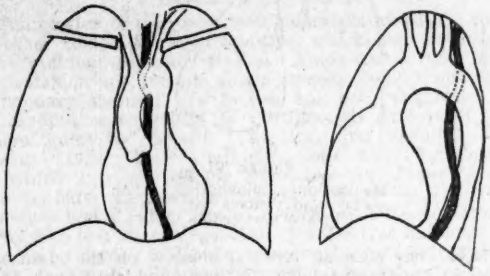

FIGURE I.
Tracing of normal aorta, showing the great vessels and the relationship of the œsophagus.

Kerley (1950) states that in the mass radiography surveys conducted in Great Britain, one subject in 80,000 is found to have coarctation of the aorta. From my own experience I should have thought the condition more common than this, having encountered 26 cases in the past five years. Most of these had been detected clinically, but seven were recognized on routine examination of chest

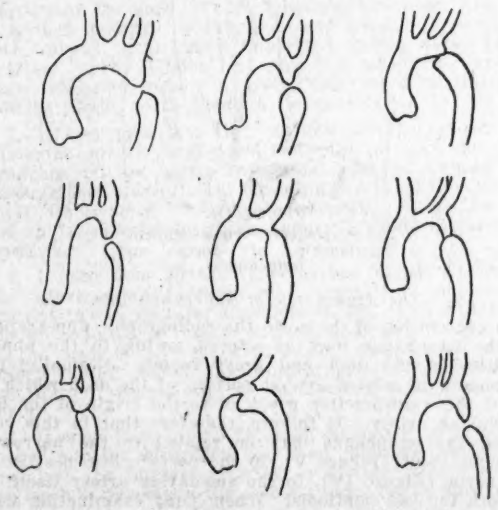

FIGURE II.
Tracing of angiograms, showing various types of coarctation seen.

films. Of the total number of 26, eight cases were found in Repatriation hospitals. This fact draws attention to another interesting aspect—namely, that the capacity for exertion is not affected for a long time. Indeed, six of these eight subjects had seen active service. All had previously had chest films taken on their admission to the forces; others had had large films taken for various respiratory disorders. I have endeavoured to find out the incidence in the Australian community as revealed by chest surveys. Unfortunately, in no States except New South Wales and Queensland had separate figures for the condition been kept. In Queensland two cases have been found in 290,000 routine chest radiological examinations, and in New South Wales the Anti-Tuberculosis Clinic has records of three in 1,250,000. I agree with the statement that the recognition of rib notching on 35 millimetre films is difficult, particularly when these are being read by the thousand, and when there is an understandable preoccupation with the lung fields. However, the point I wish to make is that diagnosis may be made on the appearances of the mediastinal shadow—a portion of the chest very well displayed in photofluorographic films, by virtue of the radiographic technique used (that is, the employment of relatively high kilovoltages).

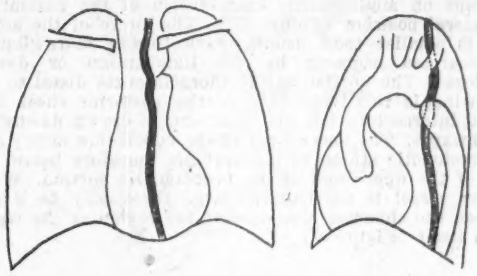

FIGURE III.
Relationship between œsophagus, left subclavian artery and coarctated segment.

Campbell and Suzman (1947) quote Fawcett as stating that one hospital autopsy in every 1000 reveals a coarctated aorta. However, Newman (1948) believes that the condition is probably more common than this and sometimes escapes detection, even at post-mortem examination.

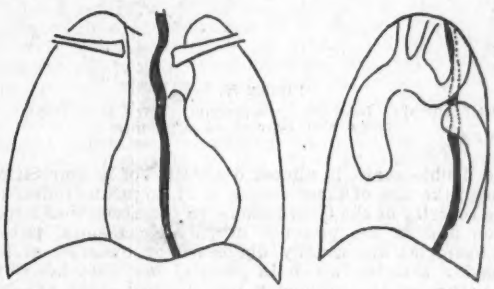

FIGURE IV.
Relationship between œsophagus, left subclavian artery and coarctated segment.

Both sexes are affected, males rather more than females, the incidence varying from 5:1 to 2:1 in favour of males. My own figures in this regard are unreliable, since few females are seen in the Repatriation hospitals, and eight cases are drawn from there.

## X-Ray Appearances.

Any understanding of the radiological features must be based upon a knowledge of the intrinsic pathology and the collateral circulation. It is proposed, therefore, to discuss all these together and not to deal with them separately.

### *Mediastinum.*

The greater part of the blood volume passes out through the innominate, common carotid and left subclavian arteries, and these vessels enlarge sometimes to an extraordinary degree. The enlargement of the left common carotid artery is usually not so prominent as that of the other two vessels, and this is in keeping with its less

important role as a collateral channel. The increased blood supply to the head and neck is stated occasionally to produce prognathism and an increase in the pulp spaces of the upper central incisors. One of our patients had the latter manifestation. In the postero-anterior chest film, therefore, the superior mediastinum may be quite broad, and I have encountered one case in which the erroneous diagnosis of a mediastinal tumour had been made (Figure IV). The left subclavian artery, in addition to being dilated, becomes tortuous, and may have a most characteristic appearance on the left side of the superior mediastinum. Below this shadow, and overlapping it in part, is the post-stenotic portion of the aorta, which may or may not be enlarged. This is continuous with the shadow of the descending aorta, which is narrow and inconspicuous. The reason for the overlapping of the two vessels is apparent on angiographic examination of the patient in the lateral position (Figure IV). The curve of the aortic arch is smaller than usual, owing to the indrawing of the coarcted segment by the ligamentum or *ductus arteriosus*. The portion of the thoracic aorta distal to the narrowing is relatively fixed to the posterior chest wall by the intercostals, but the blind end is drawn downward and inwards. The lower limit of the subclavian artery and the prestenotic stump of the aorta is therefore below the level of the upper end of the post-stenotic portion. When neither vessel is particularly large there may be a gap between the shadows representing the region of the coarctation itself (Figure V).

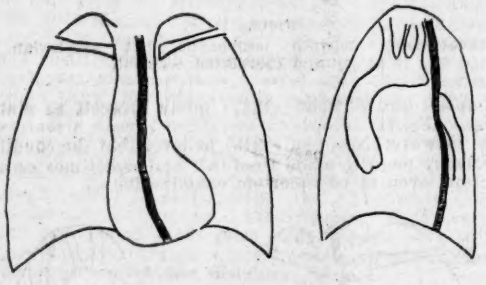

FIGURE V.
Relationship between œsophagus, left subclavian artery and coarctated segment.

The double curve is almost diagnostic of a coarctation, although the size of these vessels is by no means indicative of the severity of the obstruction. In the absence of hypertension and in the presence of palpable femoral pulses, such examples are usually diagnosed as aneurysmal left subclavian arteries, which in point of fact they are. The true nature of the pathology may be lost sight of—that the condition is a variant of a coarctated aorta in which the obstruction is only a kinking of the aortic lumen at the site of insertion of the *ligamentum arteriosum* (Figure IX). As was stated before, the tortuosity and size of the subclavian artery are not necessarily proportional to the severity of the obstruction. It is frequently stated that the dilatation of this vessel is secondary to the obstruction to the blood flow. However, I am of the opinion that it is part of the congenital anomaly and not secondary to it.

In approximately half the number of cases, however, the left subclavian artery was not apparent in the postero-anterior projection, nor was the post-stenotic portion of the aorta visible—the left side of the mediastinum being unusually straight, no prominences being seen (Figure VI). The effect of this is to make the main pulmonary artery more prominent than usual. I have encountered one case in which, because of this, the congenital anomaly was thought to be a pulmonary stenosis. While it is possible that this was an associated defect, I believe that the appearances were more apparent than real. There was no reason to suspect an associated *ductus arteriosus* or pulmonary stenosis. It appears probable that in such instances the aorta has been drawn anteriorly and medially by traction from the obliterated ductus, and so the subclavian artery and the proximal portion of the descending aorta have disappeared from view into the mediastinal shadow. The absence of the aortic knuckles and descending aorta may therefore indicate a coarctation, although these findings are obviously of no significance in infants and young children, in whom the mediastinal shadow is very variable.

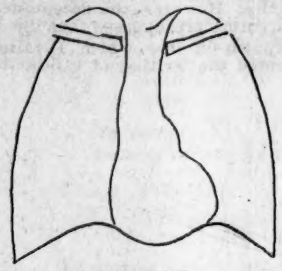

FIGURE VI.
Mediastinal silhouette, when aorta and subclavian artery are not visible.

I have once seen an unusual shadow on the right side of the mediastinum above the aorta, which I took to be an abnormal right subclavian artery. This was not confirmed by angiographic examination or operation. Campbell and Suzman (1947) report such a case. Kerley (1950) states that the descending aorta may pass down the right side of the thoracic vertebræ and to the right of the œsophagus. In the absence of rib notching, such a case would be confusing and difficult to pick on a plain X-ray film.

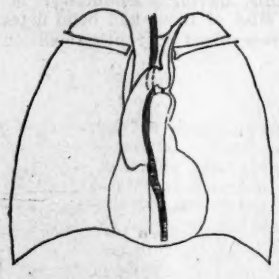

FIGURE VII.
Antero-posterior view, showing relationship of aorta and œsophagus.

*The Appearance of the Œsophagus.*

In coarctation of the aorta the radiographic appearances of the œsophagus may be altered, owing to the abnormalities in the arch and great vessels. Normally, the œsophagus is related to that portion of the arch which is about three centimetres posterior to the origin of the left subclavian artery. It follows, therefore that in this condition the œsophagus may be related to the narrowed segment itself (Figure V), to the post-stenotic portion of the aorta (Figure IV), to the subclavian artery itself, or to both the last-mentioned. When X-ray examination with a barium bolus shows no impression from the great vessels, we conclude that the œsophagus is related either to the coarcted segment or to a post-stenotic portion of the aorta which is smaller than normal. If the descending aorta is visible through the heart in the postero-anterior projection, some assessment may be made of its size, and conclusions drawn as to the possible relationship of œsophagus and stenosis.

Frequently there are two quite large impressions on the left side of the œsophagus, one above the other. Neither corresponds to the situation of a normal aortic impression, one being too high and the other too low, and this gives a lead to diagnosis. The upper impression is caused by

the left subclavian artery, the lower by the post-stenotic portion of the aorta. If this is very large the œsophagus will be displaced forwards and to the right. This indentation may blend with that caused by the left main bronchus.

### *Heart Shadow.*

In 13 of the present 26 cases there was appreciable cardiac enlargement, and this served to direct attention to the causative factors in two of the seven detected on routine radiographs of the chest. Two of the 13 patients were in frank cardiac failure, but these had been under treatment for some considerable time.

### *Associated Abnormalities.*

Coarctation of the aorta may be associated with a variety of other congenital abnormalities, which may or may not have radiological manifestations. Associated cardiac defects are common and include aortic stenosis, septal defects and pulmonary stenosis. In fact it has been suggested that, if cardiac enlargement is obvious, an associated heart lesion must be suspect (Campbell and Suzman, 1947). Abbott (1936), in 170 autopsy cases, described only six in which a patent *ductus arteriosus* was found. One of our patients successfully operated upon by Dr. H. M. Windsor had a patent *ductus arteriosus*, left-sided superior *vena cava* and bilateral cervical ribs. He also had ichthyosis and as an infant had been operated on for a strangulated bowel because of a Meckel's diverticulum. Rib notching was apparent, this being contrary to the opinion expressed that notching does not occur in coarctation when the ductus is patent (Bramwell, 1947). The main pulmonary artery was not unduly prominent, nor was there any evidence of increased vascularity of the lung fields.

I have seen one patient present with a subarachnoid hæmorrhage from an aneurysm of the circle of Willis—this apparently being a frequently associated condition.

### *Collateral Circulation.*

When the obstruction is sufficiently severe to necessitate alternative pathways, blood entering the aorta may pass through a variety of different channels to reach the lower portion of the body. These collateral channels have been described in detail by Bramwell and Morgan-Jones (1941), and anyone particularly interested should refer to the original work. Blood entering the subclavian arteries may take any of the following pathways to reach the portion of the aorta distal to the coarctation:

1. It may pass into the vertebral arteries, thence into the spinal arteries and down the spine to reach the spinal branches of the aortic intercostal arteries. These pass through the intervertebral foramina and blood thus reaches the thoracic artery distal to the stenosis. Enlargement of the spinal arteries has been known to produce transverse myelitis.

2. It may pass to the thyrocervical trunk, thence via the suprascapular, transverse cervical or subscapular arteries to the scapular anastomosis, and thence back into the thoracic aorta via the intercostal arteries. The neck of the scapula may be grooved by enlargement of the vessels in that region. Communications also occur between the thyroid vessels and the mediastinal branches of the aorta.

3. It may pass to the internal mammary arteries and thence into the superficial and deep epigastric vessels and thus into the femoral arteries, or it may return through the leash of vessels in the mediastinum and diaphragm.

Blood may pass in a retrograde fashion from the scapular anastomosis along the posterior intercostal arteries to the aorta. When this occurs these vessels enlarge and become more tortuous than usual, eroding the inferior aspect of the accompanying rib or even the superior aspect of the rib below (Figure VIII). The notchings so produced occur on those ribs related to the scapula—particularly the fourth to the eighth—and are situated several inches out from the head of the ribs.

The first two posterior intercostal arteries arise from the subclavian artery and give off branches to anastomose with the upper aortic intercostal arteries. These branches may produce medial notching of the third and fourth ribs, but the erosion of the first two is uncommon. I have never seen notching of the anterior aspects of the ribs, and can only conclude that the anterior intercostal arteries, which arise from the internal mammary artery, are not important as collateral channels.

Cases have been reported in which erosion of the ribs occurred on the right side only, and in these the coarctation lies between the left common carotid artery and the subclavian artery, or more commonly has extended proximally to involve the latter. I have also heard of another case in which angiographic examination revealed abnormal origins of the subclavian arteries, the right being involved, the left normal. It is possible that later on in life notching will be seen on the left side but not on the right.

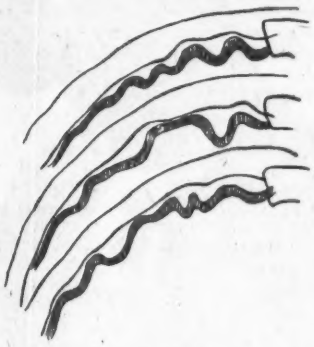

FIGURE VIII.

Tracing from an angiogram of intercostal arteries, showing rib erosion.

### Special Investigations.

Considerable information regarding the extent and location of the coarctation may be obtained in lateral Bucky X-ray films of the chest. As short a time as possible must be used at a distance of 36 inches. In interpreting lateral chest X-ray films of young adults, it must be remembered that the shadow of the descending portion of the thoracic aorta is usually difficult to see in its lower two-thirds, and this must not be taken as being indicative of a coarctated segment. My experiences with lateral tomography have been singularly disappointing, and I have never yet found it of any help in defining the site. Weinbren (1946) has had similar experiences.

Angiographic examination naturally gives most information. It may be carried out by direct injection into the aorta through a catheter or by the intravenous route. I do not propose to enter into details of either method.

### Reports of Cases.

CASE I.—B. was admitted to hospital for reassessment of his war pension, and had a routine chest X-ray examination. There was pronounced rib notching with a flattening of the mediastinal shadow on the left side. Inquiry into the previous medical history revealed that he had been discharged from the army six years previously with the diagnosis of essential hypertension. His blood pressure was 260 millimetres of mercury, systolic, and 130 millimetres, diastolic, and the femoral pulses were not palpable. A systolic murmur was audible, most pronounced between the scapulæ.

CASE II.—N. was aged twenty-seven years and was a mental defective. He was admitted to hospital for psychiatric assessment and possibly certification. A routine chest X-ray examination revealed broadening of the cardiac shadow and prominence of the superior mediastinum on both sides. There was no rib notching. The blood pressure in the arms was 180 millimetres of mercury, systolic, and 110, diastolic; the femoral pulses were palpable but weak. There was no clinical evidence of a collateral circulation. A faint systolic bruit was heard over the heart.

CASE III.—McG. had a routine chest X-ray examination (70 millimetre film) and a reexamination on a large film, and was diagnosed as having an aneurysm of the left subclavian artery. He was referred to Saint Vincent's Hospital, Sydney,

for investigation and treatment. A diagnosis of coarctation of the aorta was made on the postero-anterior chest skiagram. There was no rib notching. Clinical examination revealed a blood pressure of 130 millimetres of mercury, systolic, and 80 millimetres, diastolic, in both arms, and palpable femoral pulses. In view of these findings, the diagnosis was questioned, so an angiographic examination was performed. This revealed minimal narrowing and deformity of the aorta at the usual site (Figure IX). The blood

FIGURE X.

Coarctation of the aorta: post-mortem specimen.

pressure in the legs was found to be somewhat reduced, the systolic pressure being 110 millimetres of mercury. A faint systolic murmur was present in the chest.

CASE IV.—Bo. was aged thirty-seven years, and had a routine chest X-ray film taken. Considerable cardiac enlargement was noted, and there was a "double knuckle" shadow on the left side. There was no rib notching. Inquiry into the previous medical history revealed that twelve years previously he had been rejected for the army because of hypertension. He had had numerous medical examinations, but was regarded as suffering from essential hypertension. The femoral pulses were barely palpable. The coarctation was visible in a lateral Bucky X-ray film of the chest.

CASE V.—Di. was aged fifteen years, and had a routine chest X-ray film for a respiratory infection. His brother—a radiographer, who had taken the film—was very interested in the peculiar ribs and drew the attention of the radiologist to them. The blood pressure was 190 millimetres of mercury, systolic, and 110 millimetres, diastolic, in the arms, and 80 millimetres of mercury, systolic, and 50 millimetres, diastolic, in the legs. The coarctation was successfully resected.

CASE VI.—This patient was referred to hospital because of a retrosternal goitre detected on a chest X-ray film. The superior mediastinal shadow was broad, but this was due to vascular enlargement. There was no rib notching. The blood pressure in the arms was 130 millimetres of mercury, systolic, and 80 millimetres, diastolic, and in the legs 90 millimetres of mercury, systolic, and "750" millimetres, diastolic. A cardiac systolic bruit was heard.

CASE VII.—E., a female patient, aged twenty-seven years, was known to have some congenital cardiac lesion since the age of five years. The diagnosis was established on a routine X-ray examination. The blood pressure in the arms was 190 millimetres of mercury, systolic, and 110 millimetres, diastolic. The femoral pulses were barely palpable.

### Conclusions.

A description of the radiological appearances of coarctation of the aorta has been given, and stress is laid on the comparative frequency with which a practising radiologist may expect to encounter the condition, particularly in the reading of routine chest X-ray films.

No attempt has been made to discuss the infantile forms of coarctation, nor have many details been given on the clinical diagnosis. The pathology has been stressed, since this is believed always to be an essential part of X-ray diagnosis.

### Acknowledgements.

For permission to use patients' records, I wish to thank the Superintendent of the Brisbane General Hospital, the Chairman of the Repatriation Commission, the Superintendent of Saint Vincent's Hospital, Sydney, and Dr. I. J. McKelvie, of Ipswich. I also wish to acknowledge assistance in other respects from Dr. Harry Windsor, Sydney, from Dr. R. D. K. Reye, of the Royal Alexandra Hospital for Children, Sydney, from the Directors of Tuberculosis in all States, and from the Director of the Anti-Tuberculosis Clinic, Sydney.

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### Legends to Illustrations.

FIGURE IX.—Angiogram: subclinical coarctation.

FIGURE XI.—Branches of the subclavian artery, showing potential collateral channels.

FIGURE XII.—Normal intercostal arteries are quite tortuous.

FIGURE XIII.—Rib notching.

## VASCULAR FACTORS IN EXPERIMENTAL ACUTE PANCREATITIS.

By P. J. NESTEL, M.R.A.C.P.,

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IN any etiological classification of acute pancreatitis mention is made of the role which arterial disease may play; but its true significance is regarded as uncertain. The clinical evidence is merely circumstantial; but experiments on animals have been more convincing.

In a comprehensive review of acute pancreatitis, Joske (1955) included vascular factors only after excluding all other causes, and was then left with 17 patients who had associated atherosclerosis or hypertension.

Of greater significance was the interestingly high association between acute pancreatitis and acute coronary thrombosis found by Burn (1951).

Dunphy *et alii* (1953), in discussing acute pancreatitis following gastric or biliary surgical procedures, concluded that the main causes were temporary obstruction of the pancreatic ducts and interference with the pancreatic blood supply.

Histologically, malignant hypertension was found to produce merely small focal areas of necrosis in the pancreas (Hranilovich and Baggenstoss, 1953).

On the experimental side, the findings of Popper and his associates are of great interest (Popper *et alii*, 1942, 1948). Working on dogs, they initially ligated the pancreatic ducts to produce fat necrosis and interstitial œdema without any parenchymal necrosis or hæmorrhage. Simultaneous stimulation of the external secretions of the pancreas increased the amount of this enzyme-rich œdema fluid. Finally, by inducing a state of temporary pancreatic ischæmia, they were able to convert this non-specific interstitial pancreatitis into the acute hæmorrhagic type as seen in severe human pancreatitis. The severity of parenchymal necrosis was proportional to the degree of preexisting œdema. The conclusion reached was that interference with the vascular supply of the pancreas either rendered the cells more susceptible to injury by enzymes or in some way accelerated the activation of these enzymes.

More recently, Block *et alii* (1954) have reexamined and confirmed these findings. They worked on rats which they found to be more susceptible to the above-mentioned changes.

Apart from interference with the arterial supply, little further experimental work has been done on the vascular ætiology of pancreatitis. The role of stagnation with secondary thrombosis, such as may be produced by venous stasis, appears to have been neglected. Thrombosis of smaller vessels and capillaries has been observed to occur in acute pancreatitis; but whether this is merely secondary to the necrotizing effect of enzymes or whether it itself initiates or aggravates the necrotizing process has not been determined.

The purpose of this work has been twofold: (i) to examine the effect on the pancreas of arterial ischæmia and venous stasis, (ii) to examine the importance of thrombosis by observing the effect of anticoagulant therapy on experimental pancreatitis.

## Methods and Results.

The investigation was carried out as follows.

Albino rats of either sex, and weighing approximately 200 grammes, were anæsthetized with ether. The animals were divided into three groups for the following three sets of experiments.

### *Experiment I.*

This was designed as a control experiment, to establish the effect of (*a*) interference with the arterial supply of the pancreas, (*b*) interference with the venous drainage of the pancreas, (*c*) obstruction to the flow of pancreatic juice.

*Experiment I* (*a*).—Whereas other authors had restricted the arterial flow to the pancreas by brief periods of occlusion or by complete ligation of the arteries, in this experiment an attempt was made to reduce the arterial flow merely to such a degree that no macroscopic or microscopic damage to the pancreas resulted. This was achieved by placing sterling silver clamps on various arteries supplying the pancreas. As this would also interfere with the splenic circulation, a splenectomy was always performed. The width of the clamps which was ultimately chosen was one which satisfied the foregoing criteria. In this way it was hoped to render the pancreas more susceptible to other procedures. The clips were placed on the appropriate arteries of 15 animals, which were then sacrificed at periods varying from two to thirty days. In no instance did the animal show any ill effects, and at autopsy macroscopic examination of the pancreas showed it to be normal, and microscopic examination of the organ revealed only slight perivascular fibrosis.

*Experiment I* (*b*).—The placing of similar clamps on the main veins draining the pancreas was also found not to produce any pancreatic damage. Splenectomies were also performed. Fifteen animals were used and sacrificed as before.

*Experiment I* (*c*).—To complete the control series, the pancreatic flow was obstructed in two different ways. In the rat the pancreatic juice enters the common bile duct by several channels before the bile duct opens into the duodenum. Accordingly pancreatic obstruction was accomplished in the first instance by ligating the lower end of the bile duct. This is a standard method used by most workers and was employed on 10 animals. A further 10 animals had the bile duct tied both above and below to prevent any bile from entering the pancreatic ducts.

*Results.*—The results found were similar to the findings of other authors (Block *et alii*, 1954). There was a little fat necrosis, dilatation of the pancreatic ducts and interstitial œdema and inflammation of the pancreas. There was no parenchymatous and hæmorrhagic necrosis.

### *Experiment II.*

In Experiment II various combinations of the methods used in Experiment I were investigated. Splenectomies were performed in addition.

*Experiment II* (*a*).—Fifteen animals were used, and silver clamps were placed simultaneously on both arteries and veins. All the animals became ill within twenty-four hours, and all had died by the fifth day.

At autopsy, extensive fat necrosis and hæmorrhagic parenchymatous necrosis were found. Microscopic examination revealed a large number of thrombosed arterioles and venules. The necrotic areas were as seen in acute pancreatitis and were not merely the result of massive infarction. There was considerable œdema and polymorphonuclear exudate.

*Experiment II* (*b*).—In this experiment 15 animals were used. Silver clamps were placed on the arteries, and the common bile duct was ligated at its lower end. All the animals died within a few days, and acute hæmorrhagic pancreatitis with extensive fat necrosis was found to have occurred. The microscopic findings were the same as before, except that there was more dilatation of the pancreatic ducts.

*Experiment II* (*c*).—In this experiment on a further 15 animals the clamps were placed on the veins and the common bile duct was tied below. Acute hæmorrhagic pancreatitis resulted as before. Again it was noted that there were thrombi in some of the smaller vessels, as well as an intense degree of venous congestion.

### *Experiment III.*

The presence of thrombi in arterioles and venules was noted in the previous experiment. It was therefore attempted to prevent their formation by anticoagulant therapy, and to determine in this way, whether thrombosis was concerned in the ætiology of pancreatitis or whether it was merely the result of the general necrosis.

The procedure was carried out in two stages. As the second stage was carried out while the animals were receiving anticoagulants, a non-traumatic operation was devised.

At the first operation splenectomy was performed and a clamp was placed on the artery. The edges of the abdominal incision were not closed, but sutured to the edge of a rubber teat.

Two days later, at the second stage the top of the teat was cut off, an opening being left into the abdomen, through which the lower end of the common bile duct could be tied. The cut edges of the rubber were then approximated. Immediately after the second operation the animals were given 100 units of heparin retard gel intramuscularly twice daily. This kept the clotting time considerably prolonged. In addition to the heparin, the animals were fed "Tromexan" mixed with their feed. This maintained their prothrombin index around 30%. The administration of "Tromexan" was begun two days before the second-stage operation.

Again 15 animals were used. Of these, three died on the first day. No abnormality was detected in the pancreas, and the cause of death in all three animals was severe internal hæmorrhage. The remaining 12 survived, and when killed on the fifth day were found to be free of any evidence of acute hæmorrhagic pancreatitis. In some animals there was a little fat necrosis and dilatation of ducts, but even on microscopic examination no cellular necrosis was found. There was no evidence of any thrombosis in any vessel.

### Discussion.

It can be seen that under the foregoing experimental conditions two separate factors, local mechanical injury and anoxia, were combined to produce the desired lesion. This finds many parallels in experimental work. Anoxic liver cells are more extensively damaged by poisons. Acute renal tubular necrosis can be produced by combining ischæmia with an infusion of hæmoglobin (Rosoff, 1952), bilirubin (Nestel, 1955) or myoglobin (Corcoran and Page, 1945). Gangrenous cholecystitis may also be produced when local obstruction or chemical action is aggravated by local ischæmia (Thomas and Womack, 1952).

The degree of initial anoxia induced by clamping the artery or vein was insufficient to produce any damage. The addition of a pool of enzyme-rich fluid, which by itself could produce only minimal changes, was then followed by a highly necrotizing process in which two separate lesions, cellular necrosis and vascular thrombosis, predominated.

It is apparent that the pancreatic cells had been rendered highly susceptible to local damage, and that anoxia was the probable predisposing factor. An important point to determine was whether the anoxia was due purely to the obstruction applied or secondary to the subsequent thrombosis.

The absolute prevention of acute hæmorrhagic pancreatitis by anticoagulants seems to indicate that thrombosis of small vessels may initiate and, through a vicious circle of further thrombosis, propagate the anoxia which ultimately combines to destroy the pancreatic parenchyma.

The factors predisposing toward thrombosis were a combination of any two of three separate conditions. Diminution of arterial flow, severe venous congestion and stagnation and injury to the vessel by a locally applied proteolytic enzyme are liable to produce thrombosis in any part of the body, and it is therefore not surprising that evidence of thrombosis was found so frequently.

### Summary.

Various vascular factors which may be related to the ætiology of acute pancreatitis were investigated experimentally in the rat.

Obstruction to the flow of pancreatic juice, when accompanied by mild interference with the arterial supply or venous drainage of the pancreas, produced acute hæmorrhagic pancreatitis.

Mild obstruction to the flow of either the arterial or the venous blood of the pancreas was without effect, but simultaneous obstruction to both caused hæmorrhagic pancreatitis.

Experimental pancreatitis produced as described above could be prevented by anticoagulant therapy.

The constant finding of thrombosis of small vessels is noted and its significance is discussed.

### Acknowledgements.

I wish to thank the Superintendent of the Royal Hobart Hospital, Dr. J. M. M. Drew, for providing the facilities for this work, and Dr. C. Duncan for the photography.

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### Legends to Illustrations.

FIGURE I.—Acute pancreatitis: parenchymatous and fat necrosis produced by arterial clamp and pancreatic duct obstruction.

FIGURE II.—Recent vascular thromboses produced as in Figure I.

FIGURE III.—Prevention of thrombosis and necrosis by anticoagulants.

## Reports of Cases.

## FATAL SYSTEMIC VARICELLA: A REPORT OF THREE CASES.

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FATAL cases of varicella are rare, and comparatively few have been described in the literature. Visceral lesions in varicella were first reported by Schleussing (1927, quoted by Johnson, 1940), who described focal areas of necrosis in the liver, adrenal glands and spleen. Johnson (1940) later described a case in which there were focal lesions of a similar character in the œsophagus, pancreas, liver, renal pelvis, ureters, bladder and adrenal glands. Since then lesions have been described in the lungs, brain and kidneys by a number of authors. In the present paper the autopsy findings in a further three cases are described, with a short discussion on the main features to be expected in fatal cases.

The clinical features of Cases I and II are recorded in detail by Knyvett elsewhere in this issue, and only summaries of the clinical histories are given here. Case III is not dealt with by Knyvett, and a full clinical history is recorded.

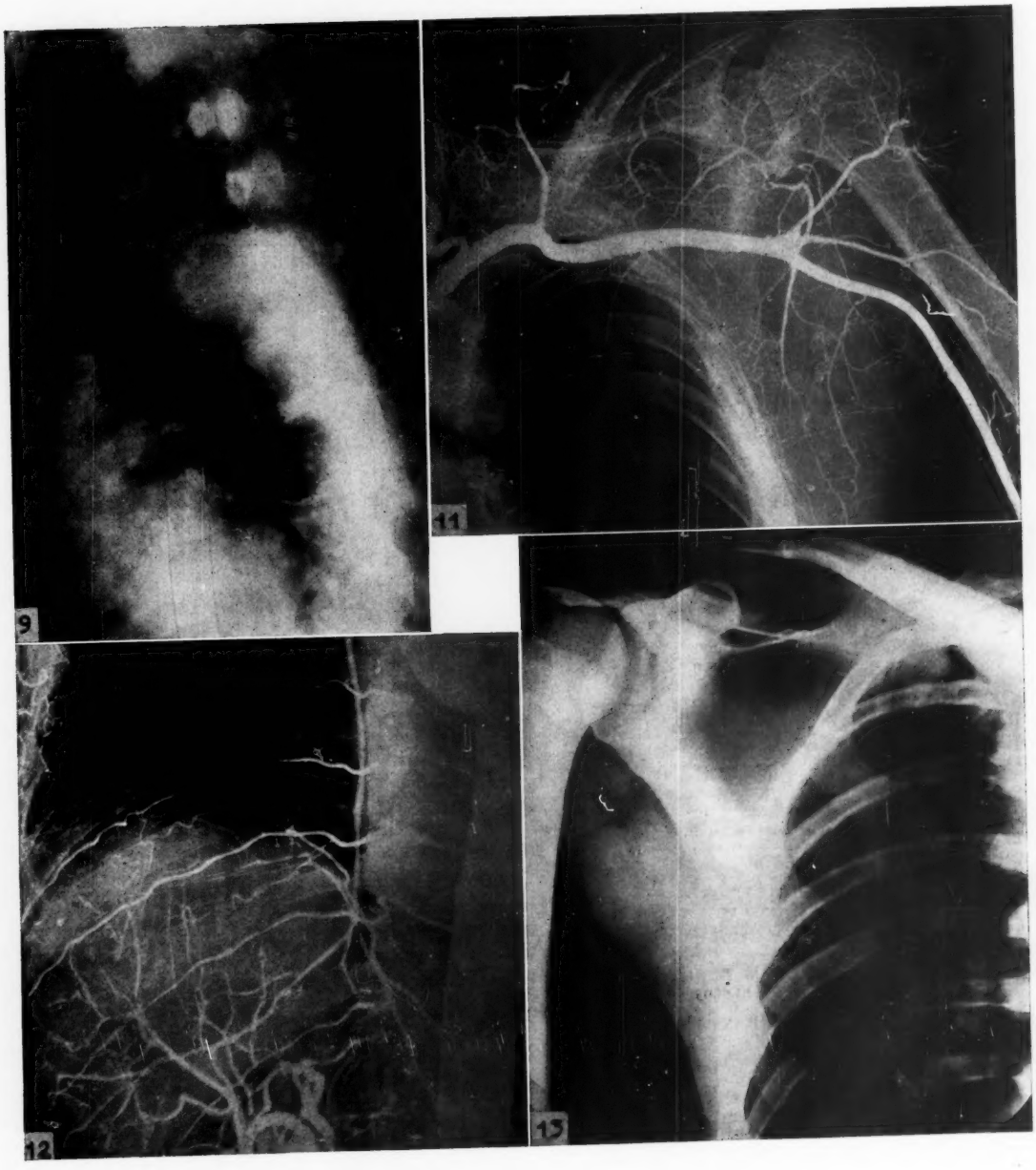
### Case I.

A girl, aged thirteen years, was admitted to hospital on September 7, 1955, at 9 a.m. in a state of delirium and in acute respiratory distress. She had been well until five days prior to her admission to hospital, when she developed varicella. Three other children in the family had or were just recovering from varicella. The patient failed to respond to treatment and died very soon after her admission.

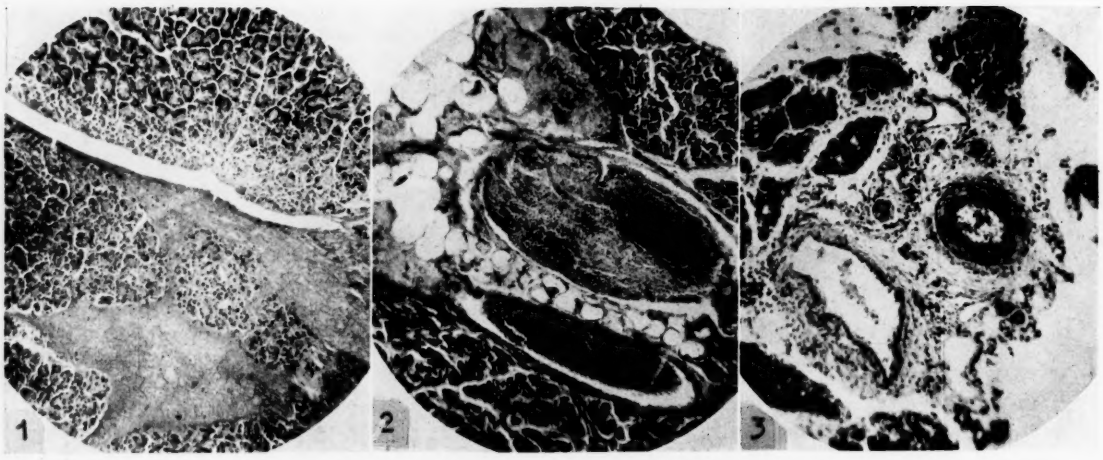
#### *Macroscopic Findings.*

At autopsy, performed twenty-four hours after death, the surface of the body had vesicles scattered over the scalp, face, trunk and both upper and lower limbs. Many of the vesicles had ruptured and had a crust of exudate on the surfaces, but many remained unruptured. Some of the vesicles had a red areola around their base. Superficial ulcerations were present in the conjunctivæ and also in the oral mucosa.

ILLUSTRATIONS TO THE ARTICLE BY J. H. HOOD.



## ILLUSTRATIONS TO THE ARTICLE BY P. J. NESTEL.




## ILLUSTRATIONS TO THE CLINICO-PATHOLOGICAL CONFERENCE.

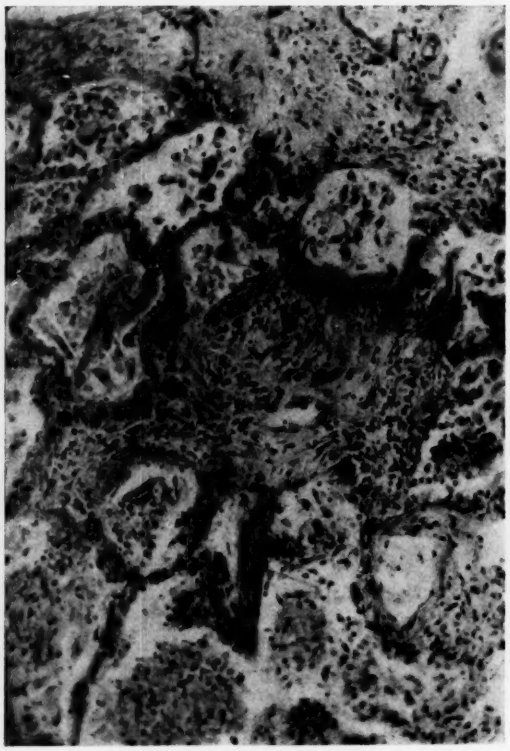


FIGURE II.
Section of lung showing areas of fibrosis with diminished number of alveoli.

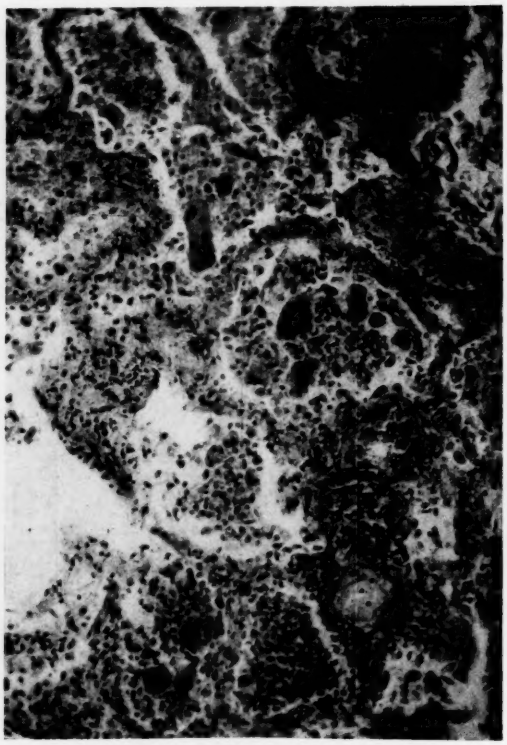
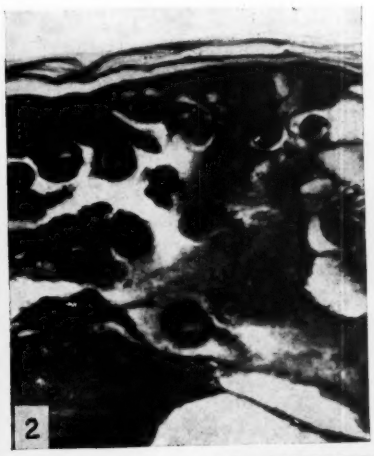
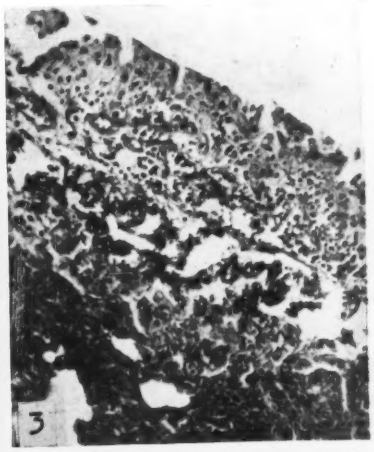


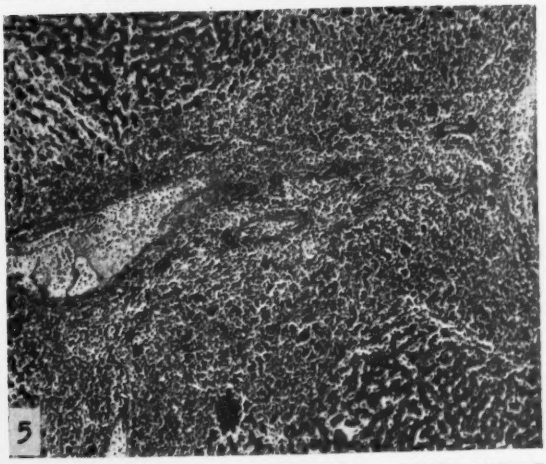
FIGURE III.
Section of lung showing alveolar walls thickened and infiltrated by lymphocytes and fibroblasts. Within the alveoli are histiocytes and giant cells.

ILLUSTRATIONS TO THE ARTICLE BY N. J. NICOLAIDES.

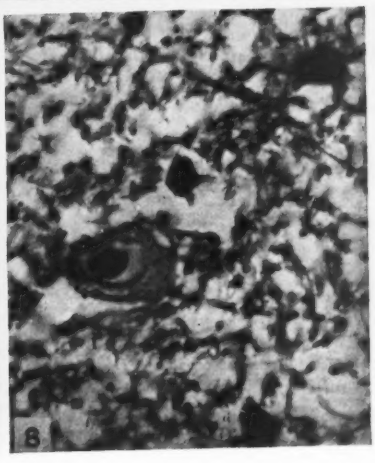



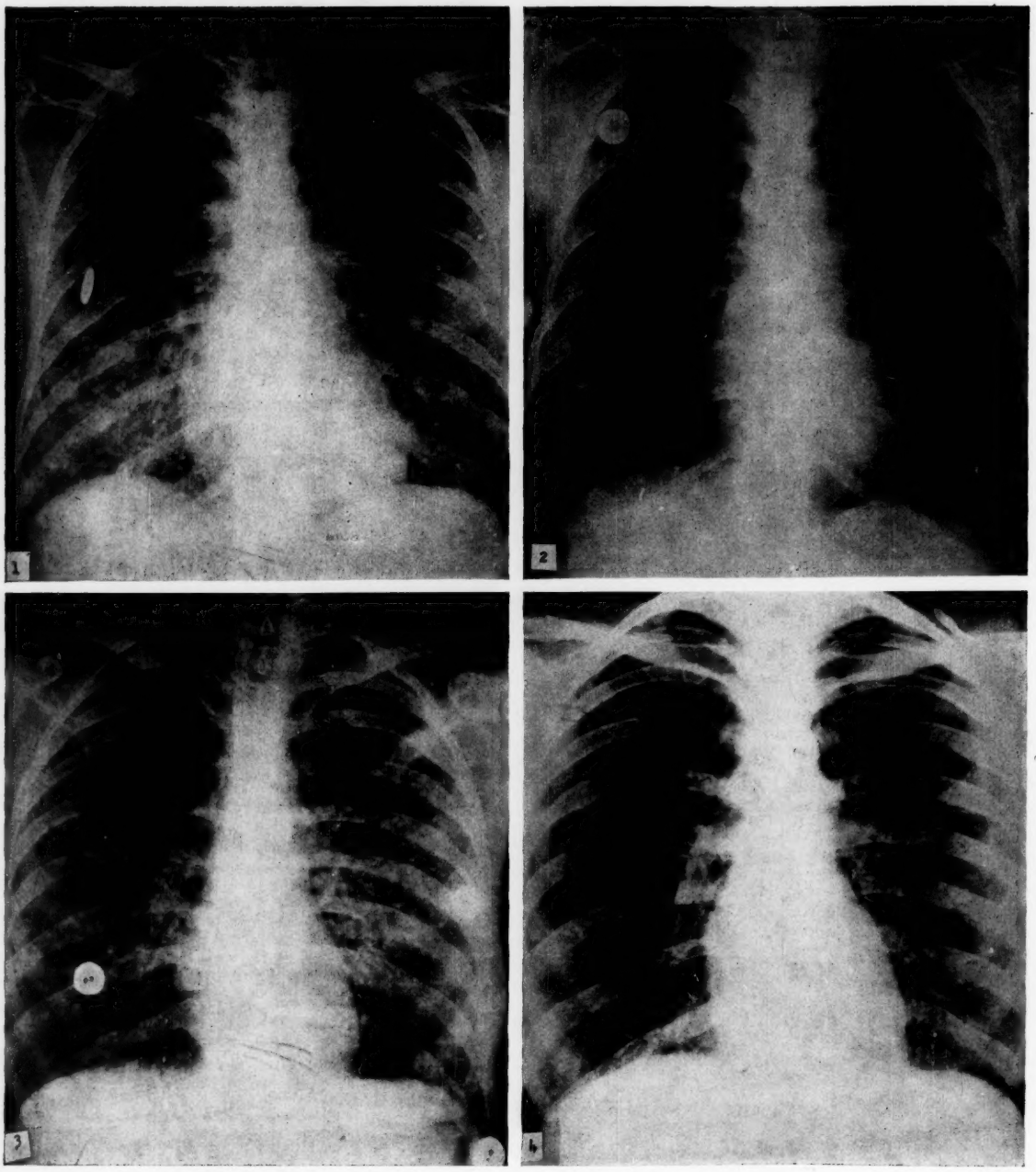






## ILLUSTRATIONS TO THE ARTICLE BY A. F. KNYVETT.



Large numbers of raised papular lesions were seen on the pleural surfaces. The outer borders of these papules were pale, but the centres were hæmorrhagic; the largest measured 0·5 centimetre in diameter. On examination of the cut surface of the lungs numerous scattered hæmorrhagic areas of consolidation were seen, the largest measuring 0·2 by 0·5 centimetre. A number of superficial erosions were seen in the tracheal mucosa. The liver was of normal size and weighed 1900 grammes. On the surface were large numbers of small petechial hæmorrhages, each surrounded by a pale areola. Examination of the cut surface of the liver revealed no macroscopic evidence of abnormality. Similar hæmorrhages were present on the surface of the spleen, but they were not so numerous as on the surface of the liver or pleura. A number of small superficial ulcerations were present in the mucosa of the œsophagus and stomach. Many small ulcerated areas interspersed with some raised dark hæmorrhagic areas were present in the mucosa of the small intestine and the rectum. Large numbers of small discrete petechial hæmorrhages, but no ulcerations, were present in the vaginal mucosa. A few small ulcerations were evident in the mucosa of the ureters and bladder. The other organs appeared normal on macroscopic examination. An attempt at blood culture made at the time of autopsy failed to yield any growth of organisms.

*Histological Findings.*

In the skin gross swelling of many of the epidermal cells had occurred. Many of the cells had swollen to such an extent that they had lost their intercellular bridges and had become separated. Some of the cells had disintegrated, with the resultant development of a vesicle (Figure I). However, lesions in all stages of development were found. Many of the swollen cells contained rounded, well circumscribed, eosinophilic, intranuclear inclusion bodies, which were approximately two to three microns in diameter, the chromatin of the nucleus being dispersed to the periphery (Figure II). Collections of cells were seen around many of the small vessels in the dermis; the cells present were mainly macrophages and lymphocytes, but some polymorphonuclear leucocytes were also present.

In the lungs there were many scattered areas of focal necrosis and hæmorrhage, with an infiltrate of macrophages, lymphocytes, polymorphonuclear leucocytes and many small particles of chromatin-like material resembling nuclear remnants in and around the necrotic tissue. Many of the alveolar walls were extremely congested and contained many macrophages and lymphocytes and some polymorphonuclear leucocytes. The septal cells were often swollen, and some of the alveoli contained a fibrinous exudate and mononuclear cells. The nodules described as being seen macroscopically on the pleural surface were found to be comprised of small areas of hæmorrhage and infiltration, with a similar cellular exudate to that described in the lesions in the lung (Figure III). Other areas of the pleura appeared œdematous, and there were many smaller scattered areas of hæmorrhage (Figure IV). A few macrophages containing intranuclear and some intracytoplasmic inclusion bodies were seen near the areas of necrosis. Some of the arteries in these areas were found to have swollen endothelial cells, and there was an infiltrate of macrophages, lymphocytes and some polymorphonuclear leucocytes in their adventitial coats. The tracheal wall was intensely congested, and was infiltrated with mononuclear cells and some polymorphonuclear leucocytes. Small areas of necrosis which contained many pyknotic nuclear remnants were present in the mucosa.

Throughout the portal tracts of the liver there were focal collections of mononuclear cells. In many areas these cells had extended into the adjacent liver parenchyma. Necrosis had occurred in many of these foci, involving the portal tracts as well as the adjacent liver cells (Figure V). These foci were infiltrated with macrophages, lymphocytes and some polymorphonuclear leucocytes and extremely numerous black granules which were thought to represent the pyknotic remnants of nuclei. Similar foci were present in the capsule of the liver overlying the areas of necrosis. Some of the liver cells near these areas of necrosis contained pink-staining intracytoplasmic inclusion bodies, and a few of the cells contained two inclusion bodies.

Similar focal lesions were present in the capsule and in the trabeculæ of the spleen, and a few were seen in the splenic pulp. They were also evident in the capsules of a number of lymph nodes.

Areas of necrosis and superficial ulceration were present in the œsophagus; these contained many pyknotic nuclear remnants and many mononuclear cells. Little inflammatory cell reaction was present in the small ulcerations seen in the mucosa of the stomach. Areas of ulceration were also present in the small bowel mucosa, and the underlying bowel wall was œdematous and infiltrated with mononuclear cells. Some areas were swollen and protruded above the surrounding bowel wall. The large bowel was involved in a similar manner.

Other organs, including the brain, thymus, bone marrow, pancreas, pituitary, heart, suprarenals and spinal cord, were normal.

## Case II.

A boy, aged ten years, was admitted to hospital on October 28, 1955, at 1 a.m., in coma. The child had developed a rash which resembled that of varicella four days prior to his admission. There were two other children in the family—twins, aged six months. One of these was still suffering from varicella, and the other had just recovered from an attack. The child died soon after his admission to hospital.

*Macroscopic Findings.*

At autopsy, performed three hours after death, the body was not jaundiced, but there were numerous skin lesions scattered over the face, trunk and extremities. The rash was mainly vesicular, but many of the vesicles had ruptured and some lesions were in the process of healing. The lesions over the face and the upper portion of the trunk had a hæmorrhagic areola around their bases. A few of the lesions were infected. No obvious lesions were seen in the conjunctival sacs, neither were any found in the oral mucosa. Small petechial hæmorrhages were present on the pleural surfaces, resembling the lesions seen in Case I. The lung underlying these pleural lesions was hæmorrhagic in appearance, but the rest of the lung did not show any obvious macroscopic evidence of pneumonic change. The liver was slightly enlarged and weighed 2000 grammes. It was yellow in colour and soft in consistency, and there were a number of petechial hæmorrhages on its surface. The cut surface of the liver also had this yellowish appearance, but the architecture appeared normal. The other organs appeared normal.

*Histological Findings.*

The skin lesions were similar to those described in Case I. Areas of congestion were seen in the lungs, and in scattered areas the alveolar walls were thickened and infiltrated with macrophages, lymphocytes and polymorphonuclear leucocytes. However, these changes were not as widespread or as severe as those in Case I, and no necrotic areas were seen. The pleural lesions were found to be similar to those in Case I. A few intracytoplasmic inclusion bodies were seen in the areas of subpleural and pleural involvement. The liver was severely affected, in that approximately the outer third of almost every lobule examined appeared grossly abnormal. The cells in these regions were swollen and appeared to have lost their cytoplasmic granulation. The cell outlines were clearly visible, and either the nuclei had lost much of their characteristic chromatin network or only their nuclear outline was still to be seen. In many of the cells the nuclei had disappeared completely. There was a little cellular exudate present, composed mainly of lymphocyte-like cells and a few polymorphonuclear leucocytes (Figure VI). Some intracytoplasmic inclusion bodies were found in the swollen liver cells, but these were few and were difficult to find. On staining with Sudan IV the cells in the outer portion of the liver lobules did not take up the fat stain to any extent; but the cells in the central portions

of the lobules were found to be filled with tiny droplets of sudanophilic material. The portal tracts were infiltrated with a scattering of lymphocytes. Examination of sections of the spleen, similar focal lesions to those described in the spleen in Case I were found. In the brain there was no evidence of perivascular demyelination or cellular infiltration or hæmorrhages. The other organs were histologically normal.

### Case III.

A man, aged thirty-four years, was admitted to hospital, comatose, on September 16, 1953. Three days previously he had developed varicella. He had had a cough since the beginning of the illness, for which he was given a sulphonamide drug and penicillin. He became comatose on the morning of his admission to hospital. Five days prior to the development of this illness one of the patient's children had developed varicella.

On clinical examination the patient was comatose and cyanosed. His blood pressure was 140 millimetres of mercury, systolic, and 90 millimetres, diastolic. His pulse rate was 130 per minute and his temperature was 100·5° F. Coarse crepitations were audible throughout both lungs. The spleen was not palpable. Both pupils were equal and small, but did not react to light. There was no neck or back stiffness, and all the limbs were flaccid. The reflexes were equal in the upper limbs, but the knee and ankle jerks could not be elicited. Both plantar responses were flexor in type. A lumbar puncture was performed and clear fluid only was obtained. On examination of the cerebro-spinal fluid, no cells were found, and the sugar, chloride and protein estimations gave normal results. On later examination the patient's plantar responses were thought to be extensor. Chlortetracycline therapy was commenced. Next day the patient's condition was worse; he was even more cyanotic and still had crepitations audible throughout both lungs. His condition later improved and he regained consciousness. X-ray examination of the chest was said to reveal shadows suggestive of extensive bronchopneumonic changes. After some slight improvement the patient's condition deteriorated again, and he died two days after his admission to hospital.

#### *Macroscopic Findings.*

At autopsy, performed approximately forty-eight hours after death, the skin lesions characteristic of varicella were present on the body; there was a discrete papular rash with vesicle formation on the face, back and trunk and on the proximal parts of the limbs. A few of the vesicles showed pustule formation.

Small pleural effusions were present, and the pleura was thickened by a film of fibrinous exudate on its surface. However, no hæmorrhagic lesions were evident on the surface as in Cases I and II. The lungs were of rubbery consistency and in cut sections a brownish-red appearance was evident. On examination, patchy consolidation with a tendency to confluence was present throughout both lungs. The tracheal mucosa was congested and was not obviously ulcerated on macroscopic examination.

The meninges were congested and the cerebral arteries were free of atheroma. Multiple hæmorrhages were seen on the cut surface of the brain; the hæmorrhages averaged up to four millimetres in diameter and were situated predominantly in the white matter. The greatest concentration was seen in the anterior part of the *corpus callosum*, where they were distributed along the lateral parts, a clear central zone being left. The *corona radiata* and internal capsule on both sides were also severely affected. There was little apparent involvement of the grey matter, and the medulla appeared normal apart from a few hæmorrhages into the pyramidal tracts in this region. The basal ganglia were also involved fairly heavily; but in the thalamus and hypothalamus and cerebellar hemispheres there were only a few scattered hæmorrhages. In the spinal cord scattered hæmorrhages were also present and were distributed predominantly in the white matter of the posterior columns. However, the grey matter was also involved to some extent. The thoracic portion of the cord was the most severely involved and the lower lumbar region the least involved. The pituitary gland was normal. The other organs were normal on macroscopic examination.

#### *Histological Findings.*

The lesions on the skin were similar to those seen in Cases I and II. Inclusion bodies were again present. The lung lesions were similar to those in Case I, although there was much more hæmorrhage into the alveoli than in Case I. In the tracheal wall there were tiny areas of necrosis, with histological features similar to those in Case I. On examination of the brain and spinal cord many small scattered areas of hæmorrhage were found. These hæmorrhages were situated predominantly in the white matter, a few being present in the grey matter. Many of the hæmorrhages were related to small thrombosed venules. Also present were some scattered areas of demyelination which were mainly perivenous (Figure VII). Little cellular exudate was present in these demyelinated areas, there being only a few large mononuclear cells. Lesions were found in the white matter of the cerebrum, the cerebellum, the brain stem and the spinal cord. Neuronal damage, where evident, was slight, and was confined to some swelling of neurons with occasional eccentric nuclei and loss of Nissl's granules. Only a few intranuclear inclusion bodies were seen (Figure VIII).

### Discussion.

In the three cases described above, the patients had all come into contact with either siblings or children who had varicella, and they all developed the characteristic skin lesions. In Cases I and II there were some hæmorrhagic vesicles. These have been described by Frank (1950) and by Lander (1955), and have usually occurred in severe or fatal cases. Cohen and Bansmer (1947) described a case of varicella with simultaneous idiopathic thrombocytopenic purpura, and suggested that most cases of hæmorrhagic varicella would turn out to be similar cases to their own if submitted to full hæmatological investigation. In our cases the course was so fulminant that hæmatological investigation was not possible. Histologically the skin lesions in the three cases were similar, and closely resembled the lesions described by Unna (1894, quoted by Johnson, 1940), by Tyzzer (1906, quoted by Johnson, 1940), by Johnson (1940), by Frank (1950), and by Lander (1955).

The lungs in Cases I and III were similar, and showed a widespread severe interstitial type of pneumonia and arteriolitis and scattered areas of necrosis and hæmorrhage. Intranuclear inclusion bodies were seen in the macrophages in Case I and Case III, and a few were seen in Case II. An interstitial type of pneumonitis was present in Case II. as in Cases I and III; however, no focal necrotic lesions were evident. The lesions in Cases I and III were similar to those described by Waring *et alii* (1942), by Oppenheimer (1944), by Leuchesi *et alii* (1947), by Claudy (1947), by Frank (1950), and by Lander (1955) in their cases. The trachea was severely involved in Case I, but only slightly involved in Case III. The pleural surfaces were involved in Cases I and II, and to a lesser extent in Case III. Pleural involvement was described by Claudy (1947) in his case, and Lander (1955) mentioned some subpleural petechiæ. Claudy likened these pleural lesions to varicella pocks.

In the liver in Case I there were many focal areas of necrosis of liver cords mainly situated in the peripheral parts of the lobules. The portal tracts were involved, and there was much infiltration with macrophages and lymphocytes, and a few polymorphonuclear leucocytes. This picture is similar to that described by Schleussing (1927), quoted by Johnson (1940), by Johnson (1940), by Leuchesi *et alii* (1947), and by Claudy (1947). The liver capsule was also involved in Case I, and in it there were areas of necrosis and hæmorrhage with cellular infiltration. In Case II there was gross damage to the liver. The cells in the peripheral parts of the lobules had undergone gross swelling with loss of their cytoplasmic granulation. Many cells had lost their nuclei and remained as ghost cells. Many of the remaining nuclei had margination of their chromatin. The cells in the central portion of the lobules

were filled with small droplets of lipoid-staining material. There was little cellular infiltration as compared with Case I, which would suggest that the stage was an earlier one than in Case I (Johnson, 1940). However, the lesions were much more widespread than in Case I, almost every lobule being affected.

The alimentary canal was involved only in Case I, and the lesions were similar to those described by Johnson (1940). The spleen was involved in Cases I and II, and then only in a minor degree, the lesions being present in the capsule and trabeculæ with a few small lesions in the pulp. The character of the lesions was similar in both cases and similar to the lesions in the liver capsules. Frank (1950) described small necrotic lesions occurring in the Malpighian corpuscles as well as in the splenic pulp.

A similar type of lesion to that in the liver and splenic capsules was seen in some of the capsules of lymph nodes examined in Case I.

Renal lesions have been described by Johnson (1940) and by Waring *et alii* (1942). When the kidneys are involved, the tubules appear to be the main site of damage, there being swelling of the epithelial cells with some mononuclear and polymorphonuclear leucocyte infiltration. Waring *et alii* (1942) called the lesion toxic nephrosis. No renal parenchymatous lesions were seen in our three cases.

The brain was involved only in Case III. The picture was that of hæmorrhagic encephalitis as described by Anderson (1953). Recently Lander (1955) described a case of acute hæmorrhagic leucoencephalitis complicating varicella, in which there were extremely widespread hæmorrhages in the white matter of the brain and spinal cord. Lander pointed out that the lesions resembled those described by Hurst (1941) under the title of acute hæmorrhagic leucoencephalitis. Waring *et alii* (1942) reviewed the reported fatal cases of encephalitis complicating varicella, and added one case of their own. They found that the usual lesions described (based on the four acceptable cases of fatal encephalitis following varicella) were diffuse perivascular demyelination in the white matter, degeneration in the ganglion cells of the brain and spinal cord, and small focal hæmorrhages. In their case, although all the above-mentioned lesions were present to some degree, they point out that the most outstanding features were petechial and ring hæmorrhages. Although the hæmorrhages in the brain in Case III do not appear to have been as severe or as widespread as in the case described by Lander, it would appear that it is a similar type of case to those described by Lander and by Waring *et alii* (1942). Blackwood (1956), in a recent discussion on the neurological complications of the acute specific fevers, draws attention to the question whether both perivenous demyelinating encephalomyelitis and acute hæmorrhagic leucoencephalitis are to be considered as common types of post-infectious encephalitis. Case III would appear to support the hypothesis that the lesions are to be regarded as variants of the same pathological process.

It would appear from investigation of these three cases, and of others from the literature, that the skin lesions of varicella must be regarded as merely one facet of this widespread disease. Visceral organs are apparently affected more often than we have hitherto realized. In most cases these visceral lesions have healed without sequelæ, but occasionally the damage to particular organs can be severe and result in a fatal termination. Should the damage be severe and yet the patient recover, sequelæ may be expected.

## Summary.

Three cases of fatal varicella have been added to the literature.

The pathological changes occurring in skin, liver, lung and brain have been described.

## Acknowledgements.

I should like to express my thanks to Dr. A. W. Pound, Director of the Department of Pathology, for his invaluable help and criticism in the preparation of this paper. I should also like to thank Dr. A. F. Knyvett for his cooperation and Dr. A. D. D. Pye for permission to use the hospital records.

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## Legends to Illustrations.

FIGURE I.—Photomicrograph showing a varicella vesicle involving the skin. (Hæmatoxylin and eosin stain, × 150.)

FIGURE II.—Photomicrograph showing the swollen epidermal cells, most of which contain intranuclear inclusion bodies. (Hæmatoxylin and eosin stain, × 1000.)

FIGURE III.—Photomicrograph showing cellular infiltration of the pleura and underlying pneumonitis. (Hæmatoxylin and eosin stain, × 150.)

FIGURE IV.—Photomicrograph showing hæmorrhage into the pleura and an underlying focus of necrosis of the lung parenchyma. (Hæmatoxylin and eosin stain, × 150.)

FIGURE V.—Photomicrograph showing a focus of necrosis and cellular infiltration in a portal tract with extension into the surrounding liver parenchyma. (Hæmatoxylin and eosin stain, × 45.)

FIGURE VI.—Photomicrograph showing swollen liver cells at the periphery of the lobules, with a scattering of wandering cells. (Hæmatoxylin and eosin stain, × 45.)

FIGURE VII.—Photomicrograph showing an area of perivenous demyelination with a scattering of wandering cells. (Hæmatoxylin and eosin stain, × 300.)

FIGURE VIII.—Photomicrograph showing an intranuclear inclusion body present in a neuron. (Hæmatoxylin and eosin stain, × 1000.)

# COMPLICATED CHICKEN-POX.

By A. F. KNYVETT,

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CHICKEN-POX is one of the most contagious of the infectious diseases, and few people escape infection in childhood. Mostly it is a minor illness that seldom requires the patient's admission to hospital, and complications, apart from secondary infection of the vesicles, are rare. However, occasionally serious and sometimes fatal complications occur. Encephalitis is the most frequently quoted one, but it is rare; pneumonia is probably more common. It is believed that the pneumonia is a specific interstitial and not an aspiration type, following ulceration of the upper part of the respiratory tract. Southcott (1953) reviewed the literature on this subject and reported a case of chicken-pox pneumonia and encephalitis.

This paper reports four severe cases of complicated chicken-pox observed in Brisbane in 1955 and draws attention to some other aspects of the disease.

### Fatal Disseminated Chicken-Pox.

CASE I.—A girl, aged thirteen years, developed chicken-pox on September 2, 1955; one sister and two brothers had had the disease in a severe form in August. Initially, the clinical course was typical. However, on September 6 she developed a non-productive cough, and at 3 a.m. on September 7 she vomited reddish slimy fluid; at this time her father noticed that she was breathing very rapidly. She was admitted to hospital at 9 a.m. on that day. On examination of the patient, she was delirious and semi-conscious, and her skin and mucous membranes were covered with the typical vesicles of chicken-pox, many of which were hæmorrhagic. Her temperature was 101·5° F. She was cyanosed, and continued to be so despite the administration of oxygen. Her respirations numbered 75 per minute, and her pulse rate was 170 per minute. The blood pressure was 115 millimetres of mercury, systolic, and 65 millimetres, diastolic. Crepitations were audible over the whole of both lung fields. There was no neck stiffness, but Kernig's sign was elicited. The right pupil was slightly larger than the left; the deep tendon flexes were present, but depressed.

A provisional diagnosis of septicæmia following secondary infection of chicken-pox lesions was made, and 500,000 units of a suspension of crystalline penicillin were given intramuscularly. One hour after the patient's admission to hospital the blood pressure reading fell to 90 millimetres of mercury, systolic, and 50 millimetres, diastolic. Ten millilitres of aqueous adrenal cortical extract were then given intravenously and intramuscularly, but without effect, and the child died at 10.30 a.m., one and a half hours after her admission to hospital.

At autopsy, the vesicular lesions of chicken-pox were present on the skin and the mucous membranes throughout the respiratory and gastro-intestinal tracts. In addition disseminated lesions were found in the liver, the spleen and the lumen and walls of the lung alveoli. The detailed pathological findings are described by Nicolaides elsewhere in this journal, but the pulmonary lesions are of great interest, particularly in view of the radiological findings in Cases III and IV. On macroscopic examination these were areas of consolidation 0·2 to 0·5 centimetre in diameter throughout both lungs. These lesions consisted of a central area of necrosis surrounded by inflammatory cells, most of which were macrophages and lymphocytes. The presence of inclusion bodies in some of these cells suggests that the lesions were of viral origin. It is interesting that, despite widespread dissemination of the lesions, there was little microscopic evidence of encephalitis.

CASE II.—A boy, aged four years, developed chicken-pox on October 24, 1955, at the same time as his brother. There were no disturbing symptoms until October 27, when severe and persistent vomiting developed, and he became drowsy. At 6 p.m. his doctor prescribed phenobarbitone in an attempt to relieve the vomiting; later in the night his condition deteriorated, and he was admitted to hospital at 1 a.m. on October 28. On examination of the patient, he was unconscious. There were many typical lesions of chicken-pox on the face and trunk; most of these were pustular, but some were hæmorrhagic. His respirations were deep and stertorous, and the respirations numbered 36 per minute. He was not cyanosed, and no abnormal sounds were heard on auscultation of the lungs. The pulse rate was 140 per minute. The liver edge was palpable two inches below the costal margin. There was no neck stiffness, and Kernig's sign was not present. The left pupil was larger than the right, and both reacted to light. All limbs were flaccid; the tendon reflexes were diminished though equal on both sides, and the plantar responses were flexor.

A provisional diagnosis of chicken-pox with encephalitis was made. At 5 a.m. generalized muscular twitching started. A lumbar puncture was performed, and clear cerebro-spinal fluid under normal pressure was obtained. At 6 a.m., thirty minutes after lumbar puncture, the patient's respiratory rate slowed suddenly to five per minute, and cyanosis developed. He was placed in an artificial respirator and his colour returned to normal, but he did not recover consciousness. He died at 7.30 a.m., six and a half hours after his admission to hospital.

Autopsy revealed the lesions of chicken-pox in the skin, the lungs, the liver and the spleen. There was extensive necrosis of the liver, and death was apparently due to acute liver failure. The pathological findings are reported in detail by Nicolaides. Again, there was no pathological evidence of encephalitis, and it is possible that the neurological symptoms and signs were due to liver failure.

### Chicken-Pox Pneumonia.

CASE III.—A married woman, aged thirty-nine years, developed chicken-pox on September 27, 1955, several weeks after one of her children. She had no knowledge of any previous attack in childhood. For the first days of illness the symptoms were mild, but on the fifth day she became delirious with a temperature of 103·8° F. She was admitted to hospital on the same day (October 2). On examination of the patient, she was cyanosed and dyspnœic. Her face and trunk were covered with the typical vesicles of chicken-pox, most of them pustular, and there were some in her mouth. She had a dry, hacking and very distressing cough. Scattered crepitations were heard throughout both lung fields. Her pulse rate was 130 per minute. There was some neck stiffness, but lumbar puncture revealed normal cerebro-spinal fluid. An X-ray film of the chest (Figure I), taken on a portable machine, showed extensive nodular consolidation throughout both lung fields.

Treatment consisted of the intramuscular administration of penicillin and streptomycin. The continuous administration of oxygen was necessary to prevent the return of cyanosis. She remained ill for two days; thereafter her recovery was rapid, and she was discharged from hospital, well, on October 15. An X-ray film of her chest taken on October 9 (Figure II) showed considerable clearing of the consolidation, and a further film on October 24 was normal. A culture of her sputum yielded a growth of streptococci and staphylococci.

CASE IV.—A married woman, aged twenty-five years, contracted chicken-pox on August 24, 1955. The rash was extensive, and vesicles appeared in the mouth. Late on the following day she developed a dry, irritating cough, and complained of retrosternal pain aggravated by coughing. On August 26 her doctor thought that she seemed very ill for uncomplicated chicken-pox, and arranged her admission to hospital that day.

On examination of the patient she had this extensive spread of vesicles, her respirations numbered 40 per minute and her temperature was 100° F. She was not cyanosed. Crepitations were audible over most of her right lung. An X-ray film of her chest (Figure III), taken on August 27, showed coarse miliary mottling distributed uniformly throughout both lungs. In this, the first case of the series, the relationship between the pulmonary lesions and the chicken-pox was not recognized, and the lung changes were thought to be due to either aspiration pneumonia or miliary tuberculosis. A Mantoux test, with a one in 1000 dilution of old tuberculin, produced a positive result, but *Mycobacterium tuberculosis* was not seen in repeated examinations of the sputum, and in addition the clinical course was unlike that of miliary tuberculosis. Two hundred thousand units of crystalline penicillin were injected intramuscularly every six hours. Her condition improved rapidly, although scattered crepitations were audible over both lungs for more than one week. X-ray films of her chest on September 5 and September 22 (Figure IV) showed considerable and progressive clearing of the mottling. A final film taken on November 11 was normal.

The patient's youngest child was admitted to hospital with chicken-pox almost two weeks after her mother. In the child the disease was mild and recovery occurred uneventfully.

### Encephalitis.

During the year 1955, only one case diagnosed as encephalitis complicating chicken-pox was seen. In this case, the cerebro-spinal fluid was normal on the patient's admission to hospital, and recovery was complete.

### Herpes Zoster with Chicken-Pox.

A connexion between *herpes zoster* and chicken-pox is now recognized. It seems probable that the same virus is responsible for both diseases. Many authors regard chicken-pox as the result of the original invasion by the virus and *herpes zoster* as an accelerated reaction in an immune, or partially immune, person (Stokes, 1955), with localization of the virus to one, or rarely more, posterior root ganglion. Nevertheless, a widespread eruption resembling chicken-pox has occurred at the same time as typical *herpes zoster* on a number of occasions (Brain, 1955). Two such cases have been seen here. The first was that of a man, aged forty-eight years, who was admitted to a repatriation hospital with typical ophthalmic *herpes zoster*. Four days after the onset of the ophthalmic *herpes zoster*, a generalized rash indistinguishable from chicken-pox appeared, and he was transferred to the Brisbane Hospital. The second was that of a man, aged seventy years, who developed a generalized rash resembling chicken-pox five days after the onset of *herpes zoster* involving the first and second thoracic segments. Neither patient could remember having chicken-pox in childhood.

### Chicken-Pox with Secondary Infection of the Vesicles.

Chicken-pox with secondary infection of the vesicles is common, and is responsible for most of the admissions to hospital. Fortunately the majority of the secondary invading organisms are sensitive to one or more of the available antibiotic drugs, and these conditions are now seldom serious.

### Discussion.

In none of these cases was the diagnosis of chicken-pox in doubt, and accordingly, virus identification was not undertaken. No drug has yet been shown to have a significant effect on the course of the disease. The chemotherapeutic agents used in these cases probably achieved little more than destruction of any secondary invaders which may have been present. This, of course, may well have been a very useful function. The two fatal cases were fulminating, and treatment had no effect whatsoever; recovery was rapid once it started in the two patients who were extremely ill.

The supposition that the X-ray findings represent a specific virus pneumonia of chicken-pox is based on a comparison of these with the post-mortem appearance of the lungs in the two fatal cases. There the microscopic findings suggested that the lung lesions were viral in origin. No X-ray films were taken of the lungs in the two fatal cases; but, had such films been taken, there seems little doubt that the appearances would have been similar to those in the cases that ended in recovery.

### Summary.

A number of cases of complicated chicken-pox are reported. The detailed autopsy findings in two fatal cases are reported elsewhere in this journal (Nicolaides, 1957).

### Acknowledgements.

I wish to thank Dr. A. W. Steinbeck for his invaluable help and criticism in preparing this paper, and the staff of the Pathology Department of the Brisbane Hospital for their cooperation. I also wish to thank Dr. A. D. D. Pye for permission to publish the case records.

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### Legends to Illustrations.

FIGURE I.—Case III: October 3, 1955.

FIGURE II.—Case III: October 9, 1955.

FIGURE III.—Case IV: August 27, 1955.

FIGURE IV.—Case IV: September 22, 1955.

## Reviews.

**The Treatment of Fractures.** By Lorenz Böhler, M.D., translated from the thirteenth German edition by Otto Russe, M.D., and R. G. B. Bjornson, M.D.; Volume II; 1957. New York and London: Grune and Stratton, Incorporated. 9¼" × 6¾", pp. 443, with many illustrations. Price: $17.50.

THE second volume of Böhler's work deals only with injuries and fractures of the hip joint and femur. They are described very fully, and reflect the advances and changes that have occurred in surgical thought during the past two decades.

There is a masterly review of dislocations of the hip joint, which is probably the most complete in the surgical literature at present. They are classified as pure dislocations and those associated with injuries to the adjacent bones. In contrast with British practice, Böhler allows early movement and weight-bearing after a pure dislocation. He states that he has not seen avascular necrosis of the femoral head occur as a result.

Fractures of the neck of the femur receive special attention. Accounts of the earlier methods of treatment are given and indications for their employment; these include the abduction plaster of Whitman and extension.

When nailing is employed, accurate reduction of the fracture and perfect central placement of the pin are insisted upon. The direction finder, which is new to British literature, appears to ensure this. Here again Böhler differs from accepted British practice; weight-bearing is allowed after two weeks.

The use of the Küntscher nail in selected cases of fracture of the shaft of the femur is advocated; such treatment for pathological fractures of the shaft, due to secondary neoplasm, is in keeping with advanced surgical thought in Britain and America. A good description of the technique of this procedure is given, and is especially helpful; it shows how to avoid the pitfalls of this technically difficult procedure.

The management of gunshot wounds of this region is an excellent feature, and reflects the great experience and wisdom of this surgeon.

Like the first volume, this book is excellently produced and profusely illustrated. It will prove to be a surgical classic.

**Sequeira's Diseases of the Skin.** By John T. Ingram, M.D. (Lond.), F.R.C.P. (Lond.), and Reginald T. Brain, M.D. (Lond), F.R.C.P. (Lond.); Sixth Edition; 1957. London: J. and A. Churchill, Limited. 9¾" × 6", pp. 856, with 63 coloured plates and 426 text figures. Price: 105s.

IT is ten years since the last edition of this book appeared. A year after the fifth edition was published, Dr. Sequeira died, and this new publication becomes the responsibility of two of his most famous pupils, Dr. J. T. Ingram and Dr. R. T. Brain.

There is a certain amount of sentiment in reviewing "an old friend", and we are struck by the number of illustrations that appeared in the 1919 volume and are still retained in the 1957 edition. It would be difficult to improve upon the "black and white" illustrations, but a few of the coloured plates could be replaced. For the purpose of comparison, there is an increase of 43 illustrations over the last edition, making in all the total of 489. Some of these are from "The Institute of Dermatology", and are of very high order from both the clinical and the histopathological aspects. Special mention must be made of those dealing with *molluscum sebaceum*, now correctly diagnosed.

Much that was stated in the review of the fifth volume could also apply to this one. It is not a complete work on dermatology, in comparison with some of the larger American text-books; but it is the most comprehensive work produced in the British Empire. All the common diseases are well described, with emphasis on diagnostic and therapeutic measures. In fact, much has been rewritten, and although the references are not diffuse, they are in the main recent, and include the names of some Australian dermatologists. A sincerity and an absence of "packing", such as one would expect from such distinguished English dermatologists, are evident.

Australian dermatologists, who are particularly trained in the treatment of cutaneous neoplasms, will be pleased to note that this new edition has much more to say about

X-ray therapy and less and less about the use of radium plates.

This work is right up to date, and can be highly recommended without reservation to those practitioners who are interested in diseases of the skin.

**The Child and the Family: First Relationships.** By D. W Winnicott, edited by Janet Hardenberg, M.B.; 1957. London: Tavistock Publications, Limited. 8¼" × 5¼", pp. 158. Price: 12s. 6d.

WHEN an expert in child psychiatry who is also a psychoanalyst succeeds in writing a simple, lucid book for mothers, it is well worth the attention of the medical profession. As Dr. Winnicott says, "a writer on human nature needs to be constantly drawn towards simple English and away from the jargon of psychologists". He has therefore tried to explain to the "ordinary devoted mother" some of the mysteries of the mind of her child revealed by psychoanalysis and in his everyday management of behaviour problems. So well does he do it that we are not aware of any mystery, and every mother will be reassured and encouraged by reading this book.

The book is made up of a number of broadcast talks rewritten for publication. It covers many of the early worries of mothers, such as the following: "Why do babies cry?"; "Getting to know your baby"; "Instincts and normal difficulties". Several chapters are given to the psychological aspects of infant feeding. "Infant feeding is a matter of infant-mother relationship, a putting into practice of a love relationship between two human beings." Dr. Winnicott stresses how easily this delicate relationship is disturbed by unsympathetic and dictatorial medical and nursing supervision, and how important it is to preserve and develop the maternal instinct.

The book is in two parts, the first dealing with the relationship between mother and child, and the second with family affairs. The second part includes chapters on father, twins, adoption, the only child and visiting children in hospital. Though it is difficult occasionally to accept some of the phantasy world of the psycho-analyst, most of the book is delightfully human and related to everyday living and loving, and is full of the sincere wish of its writer to help and support normal parents. It will therefore be a useful addition to libraries of doctors who like to be able to lend a helpful book to the thoughtful, conscientious mother who is apt to worry a little too much. It is to be hoped that health centre sisters will have an opportunity to read it, and child study classes will certainly welcome it.

**The Pathogenesis of Coronary Occlusion.** By A. D. Morgan, M.A., M.D.; 1956. Oxford: Blackwell Scientific Publications. 9¾" × 7¾", pp. 182, with 179 illustrations. Price: 42s.

THIS fine monograph from the consultant pathologist to the Westminster Hospital consists of two parts. In the first the literature of coronary atherosclerosis is reviewed in the light of the thrombogenic hypothesis. The author does not adequately define his terms; but his protagonistic approach makes this lively reading, as he has his own champion Rokitansky almost breathing over Virchow's shoulder as the latter writes, and Jenner languidly waiting for Hunter to die. It is surprising to find no reference to three such standards as the main works of Blumgart, Prinzmetal (on collaterals) and Hueper (on anoxic theory). Contrariwise, the inclusion of the half-page Chapter X on cardiac hypertrophy and electrocardiography invites criticism. The real substance of the work is in the second part, where more than half of the first 80 pages are filled with quarter-page photomicrographs depicting the morphology of coronary artery occlusion. The quality of this will appeal as first class, even to those who are bothered by the contentious bone Dr. Morgan never ceases to worry. The three chapters of six pages on "Correlations" consist mainly of various tables for which the material is scanty, incomplete and inconclusive. Thus the blood pressure was recorded in only 15 of the 40 cases studied. In a bibliography of some 350 works dating from 1649 to 1956, slightly more than one-third belong to the decade prior to publication. There are author and subject indices.

Of the various sections, that on the episodic and serial deposits on the intima and the recurrent "layering" is perhaps the best, but the author is apparently not aware that this same phenomenon, referred to by others as "stratification", "lamellation" *et cetera*, occurs in the artificial cholesterol-induced atheroma of herbivora. The exposition of intimal vascularity is beautifully clear, though very teleological; but that of intimal hæmorrhage is rather less cogent than that of Paterson himself or that of Horn and Finkelstein. The author has a rather quaint explanation of some features of arterial thrombosis; but his views on clot retraction *in vivo* are shared by some British colleagues, although perhaps they would question that its force could disrupt intimal layers, as stated in Figure 82. The section on fibrin in atherosclerotic plaques is the epitome of histochemical faith. The author uses six staining methods for his serial sections, and refers to the "tinctorial reaction" of the tissues.

The chapter on coronary occlusion and myocardial infarction reveals the major weakness of this work, for methods and materials do not match. Of the 40 cases used, 26 were coroners' cases of sudden death; only 12 of these showed a total occlusion, only 11 showed an infarct, and 10 showed neither. In 20 of the 40 a total occlusion was present, and in all there were only 26 total and 13 subtotal occlusions. It seems a pity that Dr. Morgan apparently eschews the injection techniques. His views on coronary atheroma of fifty years ago will be challenged; but for some years few have doubted his main conclusion, *viz.*, that the major occluding process is thrombosis, although many will disagree with arguments used here to prove it.

In the generous foreword Professor Duguid has extended his *imprimatur* to this work; but his tentative opinion of it as a "decisive study" is not substantiated by the author's Procrustean efforts in "Revaluations" and "Conclusions" to reconcile all theories. This valuable contribution merits close study by those with a special interest in this difficult and contentious aspect of vascular pathology. It is perhaps less valuable to the clinician unfamiliar with minutiæ, and confusing rather than instructive for the student. It is edifying to both thinkers and doers in this field.

The publishers have done their work handsomely, if somewhat extravagantly.

## Books Received.

***[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]***

"The Principles of Therapeutics", by J. Harold Burn, M.A., M.D., F.R.S.; 1957. Oxford: Blackwell Scientific Publications. 8¾" × 5¼", pp. 288, with 35 illustrations. Price: 27s. 6d.

The author is Professor of Pharmacology in the University of Oxford.

"Clinical Roentgenology of the Digestive Tract", by Maurice Feldman, M.D.; Fourth Edition; 1957. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 10" × 7", pp. 802, with 728 illustrations. Price: £8 5s.

Extensively revised since the previous edition of 1948.

"Chronic Bronchitis in Newcastle-upon-Tyne", by A. G. Ogilvie, M.D. (Dunelm), F.R.C.P. (Lond.), and D. J. Newell, M.A. (Cantab.); 1957. Edinburgh and London: E. and S. Livingstone, Limited. 8¾" × 5¼", pp. 127, with tables and illustrations. Price: 15s.

The result of a comprehensive survey.

"Some Milestones in the History of Hematology", by Camille Dreyfus, M.D.; 1957. New York and London: Grune and Stratton, Incorporated. 9" × 6", pp. 96, with illustrations. Price: $4.50.

Not a formal history, but a series of landmarks and milestones from ancient times to our own.

"The Development and Disorders of Speech in Childhood", by Muriel E. Morley, B.Sc., F.C.S.T.; 1957. Edinburgh and London: E. and S. Livingstone, Limited. 8¾" × 5¼", pp. 458, with 90 illustrations. Price: 45s.

The author is Speech Therapist-in-Charge of the Speech Therapy Unit, the United Newcastle-upon-Tyne Teaching Hospitals and the Newcastle-upon-Tyne Hospital Management Committee Group.

"Diabetes Mellitus: With Emphasis on Children and Young Adults", by T. S. Danowski, B.A., M.D.; 1957. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 9" × 6", pp. 534, with many illustrations. Price: £7 8s. 6d.

Based on extensive experience in the management of diabetic children.

The Medical Journal of Australia

SATURDAY, JULY 20, 1957.

*All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.*

*References to articles and books should be carefully checked. In a reference the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those adopted by the Quarterly Cumulative Index Medicus. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.*

*Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.*

## THE TENTH SESSION OF CONGRESS: A REMINDER.

THE Hobart Congress is rapidly coming nearer. Our colleagues in Tasmania are bending their backs to the heavy task with energy and imagination, and it is time that we all gave heed to the matter. It was no little thing for the profession in our smallest State to accept responsibility for a Congress, and out of the 200 or so doctors who make up Tasmania's total medical population only about 100 are involved in the actual organization. Since the Congress is being held in Hobart, most of the work inevitably will fall on those who are on the spot, and it appears that practically all the doctors in Hobart are busy on some aspect to make Congress a success. If the remainder of the ten thousand or so doctors in Australia put their great weight behind this effort, the Congress would be a staggering success. Not, of course, that anyone expects the whole ten thousand and their wives and families to invade Hobart next year. Tasmania is not a very large island, and Mount Wellington limits the inland expansion of Hobart in any case. Nevertheless, the Tasmanians will be pleased to welcome as many as they can fit in. Elsewhere in this issue, under the heading "Congress Notes", will be found a warning about accommodation. Wool sales will limit its availability in the week preceding Congress, and the Executive Committee advises members to arrive just before Congress starts. The best hotels are already either full or rapidly being filled, but a good deal of other acceptable, if less formal, accommodation should be available.

Most of those who have thought of the matter are looking forward to this Congress with delight. Hobart has great charm, and Tasmania is an excellent place for a summer holiday incorporating a week at Congress. A first-rate scientific programme is being prepared, and it is hoped that it will appeal to all members of the profession, varied though their interests may be. The social programme is well in hand. Perhaps most important of all, the opportunity to meet old friends, to make new friends and to exchange views on professional and personal matters comes to the medical profession as a whole only once in three years. The corollary is obvious: write without delay to your Local State Secretary for an application form for the Tenth Session of the Australasian Medical Congress (British Medical Association) to be held in Hobart from March 1 to 7, 1958.

## PRIVATE CONSULTING ROOMS AT PUBLIC HOSPITALS.

THE recent opening of the Royal Prince Alfred Hospital Medical Centre in Sydney brings into the spotlight an important development in medical custom. For the past quarter of a century, especially in North America, it has become increasingly common for doctors to have their private consulting rooms close to the public hospitals which they visit. According to C. Rufus Rorem,[1] a majority of such hospitals in the United States originally established the private consulting rooms by remodelling or renovating a section of a building which had been designed for other purposes. In some cases private rooms not otherwise required have been set aside for consulting rooms, and in subsequent building extensions provision has been made for this need. In other cases existing adjacent buildings have been renovated or new buildings have been constructed to provide blocks of medical consulting rooms. These projects have been financed either from hospital funds or as commercial ventures, the property being owned by partnerships, insurance companies or real estate firms, and the tenants pay an appropriate rental. At some hospitals an attempt is made to establish and maintain a balance of professional specialties among the occupants of the private offices. However, in America the idea seems to have been most popular with surgeons, obstetricians and other specialists who put a high percentage of their patients in hospital; pædiatricians, psychiatrists and dermatologists are usually less interested. Some doctors also conduct practice in other locations, but many with "down-town" rooms ultimately relinquish them. The usual practice seems to be to make maximum use of the hospital facilities for laboratory work, radiography and other specialized aspects of diagnosis and treatment; in some cases it is obligatory to do so, and in others doctors may not carry out these specialized services at their rented rooms, whether or not they use the hospital facilities.

The idea has its critics and its enthusiastic supporters. Apart from the differences of opinion that arise about how such a venture should be financed, a matter which is essentially domestic and varies from hospital to hospital, most of the faults that are found seem to apply only when

[1] *Modern Hospital*, March, 1957.

the doctors' rooms are in the hospital building. When the system of having a separate building is adhered to, the advantages seem to be many, and this was the system adopted after careful consideration by the Board of Directors of the Royal Prince Alfred Hospital. The chief advantages were referred to by Sir Herbert Schlink, Chairman of the Board, at the ceremony on May 23, 1957, when the Medical Centre was officially opened by His Excellency the Governor of New South Wales. The first advantage listed by Sir Herbert Schlink is the saving of travelling time—a significant factor in a city with such traffic problems as Sydney has. This means more frequent visits, especially to dangerously ill patients, and ready availability of the visiting staff in emergencies. The second is the effect on the members of the resident medical staff, who not only have a more mature opinion at hand when required, but also are stimulated to better work by the more frequent contact with their chiefs. Then there is the improvement in undergraduate teaching, because the consultants can afford to spend more time with their students. At the same time, there is greater opportunity for clinical research, especially on the part of young consultants whose private practice has not grown sufficiently to keep them fully occupied in their rooms. Finally, the doctors themselves have the advantage of stabilized rentals under the control of a Hospital Board which is not likely to exploit them, and the ready use of hospital facilities for diagnosis.

It must be agreed that this system is not in its final form. Further experience will no doubt show weak points in it to be rectified, and particularly good points to be developed. The reaction of the private patients is yet to be seen fully, although a year's experience at the Royal Prince Alfred Hospital Medical Centre suggests that it will be favourable. That the system could be abused and many of the advantages listed by Sir Herbert Schlink cancelled out by laziness or indifference on the part of individual members of a visiting staff cannot be denied, though we feel justified in regarding it as unlikely. However, it will do no harm to reflect on the concluding paragraph of Rorem's article:

> It is essential that no improper professional or financial advantages be enjoyed by occupants of private offices at community hospitals. Likewise, the economic advantages of the arrangement should be shared with the patients who receive service and the public which provides the facilities. In the long run, this movement must be evaluated according to its effect upon the quality of medical care.

Meantime we offer our congratulations to the Board of Directors and the visiting staff of the Royal Prince Alfred Hospital on their vision and enterprise, and suggest that other hospitals may follow suit. If it is possible, we hope that government agencies may make money available for this progressive move where it is not otherwise likely to be forthcoming.

# Current Comment.

## ACUTE NON-SPECIFIC PERICARDITIS.

THE terms acute non-specific pericarditis, acute idiopathic pericarditis, acute benign non-specific pericarditis, acute pericarditis of the benign type, acute relapsing pericarditis, fugitive pericarditis and cryptic pericarditis are all synonyms for the same disease, according to M. L. Gelfand and L. Goodkin.[1] It is a benign disease of acute nature, having frequent recurrences and usually ending in complete recovery. It affects males more than females in a ratio of three to one; and although no age group is exempt, it is more often observed in the second to fourth decades. Gelfand and Goodkin state that the exact ætiology of this condition is obscure, but since over 50% of those affected give a history of previous upper respiratory tract illness, a virus may be responsible. The allergic theory has its supporters, who contend that the body becomes sensitized to a previously invading organism or its toxic products, and that the antigen-antibody reaction thus initiated results in pericarditis. Others are of the opinion that its close resemblance to rheumatic fever would speak for a similar genesis. In the very early stages of this disease, some people may appear quite ill, and occasionally the condition may even be ushered in by peripheral collapse with cardiac arrhythmia; this makes it difficult to differentiate from a more serious cardiac disorder, such as myocardial infarction. In a short time, however, the patients rally and the disease takes on the appearance of benignity, despite the laboratory and electrocardiographic abnormalities suggesting serious involvement. The outstanding complaint is pain in the chest; this is described as a heaviness, a tightness, or a knife-like or constricting pain aggravated by bodily motion and respiration, and radiating upward towards the neck and shoulders and downward to either hand or to the abdomen. Because of the nature of the pain, the condition may be mistaken for pleurisy, pneumothorax, an acute abdominal emergency or acute coronary occlusion. In fact, acute coronary occlusion and non-specific pericarditis are often so extremely difficult to differentiate on the basis of pain alone that only time and careful attention to the clinical progress and the laboratory data can clarify the situation. Fever is nearly always present, and a pericardial friction rub is helpful when present, but in its absence the diagnosis must be based upon other evidence. Cardiac enlargement is frequently noted in this disease, being due either to fluid in the pericardial sac or to dilatation of the heart. As a result dyspnœa and orthopnœa may develop, to disappear as the infection subsides. Pleural involvement and lung infiltrations are seen in about 50% of cases of pericarditis of the non-specific type. Leucocytosis and increase in the sedimentation rate appear early in the disease; the former returns to normal as the acute infection subsides, but the latter persists for a long time even in the presence of complete recovery. Recently the transaminase level in the blood has been shown to be normal in pericarditis, but considerably raised in myocardial infarction, and this may prove to be an extremely useful laboratory aid in differentiation of the two disorders. The most important clue in the recognition of non-specific pericarditis would appear to be the serial electrocardiographic changes observed during its course.

There is no definite therapy for idiopathic pericarditis, although the literature contains reports on the use of various antibiotics and ACTH in its treatment. Since all patients recover completely without sequelæ, it is difficult to make an accurate assessment of any specific remedy. Gelfand and Goodkin have employed symptomatic therapy, with antibiotics where indicated, especially when pulmonary signs became manifest, and their results are stated to be in no way different from those reported by other observers from the use of any specific agent. They present clinical details of five cases. The patients were all males, and the ages varied from twenty-four to fifty-two years. Two gave a history of previous respiratory infection, and two had undergone some emotional strain. The condition of three presented a benign aspect throughout. The duration of the disease varied from two weeks to almost two months, and the clinical features common to all consisted of pain in the chest aggravated by breathing and movement, chills and fever, mild leucocytosis at the outset lasting for a variable period of time, and persistent elevation of the sedimentation rate even after the patient had

[1] *Ann. Int. Med.*, September, 1956.

apparently recovered. Cardiac enlargement with subsequent reduction in size, demonstrable by X-ray examination, was observed in three instances, and in these same patients pleural and pulmonary abnormalities were also present. Recurrences developed in three cases, bradycardia in two, and auricular fibrillation in one. Profuse sweating was a common complaint. The characteristic pericardial friction rub, which is considered to be associated with 60% to 75% of all cases of acute non-specific pericarditis, was absent in four cases of this series.

The close resemblance of the clinical picture in three of the patients to that of acute myocardial infarction led to the use of anticoagulants early in the course of the disease, but this therapy was interrupted as soon as the diagnosis of pericarditis became apparent. A rheumatic ætiology was suspected at the outset in two cases because of the age of the patient, the presence of arthralgia and the discovery of a raised antistreptolysin titre. The electrocardiograms of the entire group were consistent with what may be observed in pericarditis. Although initially several of the electrocardiograms were interpreted as being consistent with myocardial infarction, nevertheless, it was thought that the clinical picture as well as the serial changes and the return of the abnormal alterations to their original status favoured the diagnosis of acute non-specific pericarditis.

Gelfand and Goodkin state that the diagnosis of acute idiopathic pericarditis should be made on the basis of the clinical criteria and the serial electrocardiographic changes characteristic of the condition. Failure to detect a pericardial friction rub does not necessarily invalidate the diagnosis, especially since at times this may be missed. Familiarity with this clinical syndrome is most rewarding, both in its own recognition and in its differentiation from acute myocardial infarction, which it closely resembles.

## THE ACETYLCHOLINE TEST FOR SUSCEPTIBILITY TO COUGH.

R. TIFFENEAU, of Paris, made a valuable contribution to clinical respiratory physiology when he added the measurement of the volume of gas expired in the first second of a forced expiration to the tests of ventilatory capacity. Another useful test employed by Tiffeneau and other French workers is based upon the inhalation of acetylcholine: a significant reduction in ventilatory capacity occurs in asthmatic subjects and others liable to "bronchospasm". This test more often yields a positive response than a test which employs a bronchodilator drug, and in France it is thus considered to be the more sensitive indicator of reversible bronchoconstriction as a likely factor in the development of symptoms in various chronic respiratory disorders. Tiffeneau has now described[1] another test based upon the production of cough in susceptible subjects by the inhalation of acetylcholine of about 1% strength. Evidence is produced to show that this action, which is largely independent of that upon ventilatory capacity, is due to the excitation of sensory nerve endings in the bronchial tree. The "cough action" is manifest within ninety seconds of beginning the inhalation and ceases immediately the aerosol is discontinued. The effect on ventilatory capacity, if any, persists for fifteen to thirty minutes, although any wheezing which is produced can be easily relieved by an adrenaline aerosol. The development of cough may be prevented by the prior administration of several drugs, and in fact the suggested mechanism of production of the cough is based upon pharmacological observations of this type. No cough is produced in normal subjects, although during transient acute inflammatory diseases of the respiratory tract the response to the test becomes positive. According to Tiffeneau, acetylcholine inhalation always produces coughing in patients with emphysema. A persistently positive response is interpreted in any circumstances as indicating "an increased sensitivity to all exogenous irritants" which "does not signify a favourable prognosis". There is no question of an allergic basis for the reaction: positive findings will be at least as common in chronic bronchitis as in asthma, although the concomitant fall in ventilatory capacity is likely to be proportionately much greater in the latter condition.

These observations are interesting, although in individual cases the test seems to offer little more than could be gauged on clinical grounds. Perhaps it emphasizes the practical value of the simple, but often neglected, advice which is frequently helpful to patients with chronic cough or wheeze: clear the bedroom and cover the pillows. Tiffeneau suggests that a positive response to the test may be considered grounds for pre-operative antibiotic therapy, for delaying operation or for modifying the choice of anæsthetic agents; but one suspects that few surgeons would be deterred by one or two artificially produced and unproductive coughs. On the other hand, Tiffeneau deserves support when he advocates a large-scale, and presumably long-term, investigation into the value of the test in detecting those workers who are likely to develop symptoms in dusty atmospheres. There is a real need to tackle this increasingly important problem, and no other method of approach has been put forward. It would even seem reasonable to exclude those workers whose ventilatory capacity was significantly reduced.

Perhaps the most useful role of the test may lie in the evaluation of drugs which are intended to reduce cough. Tiffeneau claims that this can be done by determining, for example, the threshold concentration of acetylcholine required to produce cough before and after the administration of such a drug. A simple method of assessing the efficacy of antitussive agents in human beings, adaptable to comparative studies, has long been required. If the test should prove useful from this standpoint alone, all who have to treat coughs symptomatically will be grateful to Tiffeneau's originality.

[1] *Dis. Chest*, April, 1957.

## INFANTILE ARTERIOSCLEROSIS.

ARTERIOSCLEROTIC CHANGES of significant degree are not common in young children, but they occur often enough to be kept in mind. R. A. Lyon and S. Kaplan, writing in Nelson's "Textbook of Pediatrics",[1] refer to several forms in which arteriosclerosis may be found in childhood. They point out that at this stage the type of arteriosclerosis common in subjects of advanced ages may have its beginning. Atheromatous patches consisting of deposits of fibrin and fat within the intima of the aorta and larger arteries have been noted in older children and in young adults, in association with rheumatic fever, diabetes and nephritis; they rarely cause symptoms. The most serious type of vascular disease in childhood is described as a sclerosis of the arterioles or malignant hypertension which produces high blood pressure and is invariably fatal. Its ætiology is unknown. It is most apt to occur in late childhood, but may occur in infancy.

In varying degree calcification and sclerosis of the arteries in infants and young children may be encountered in a number of clinical conditions. These have been considered, primarily from the radiological viewpoint, by H. S. Weens and C. A. Marin,[2] who state that foremost among these are disorders in which disturbances of the calcium and phosphorus metabolism play an important role. Thus infantile arteriosclerosis has been recognized in renal disease, hyperparathyroidism and vitamin *D* intoxication. Similar arterial changes have also been noted in progeria, in which the arteriosclerotic process is associated with extensive growth disturbances and profound metabolic changes. Aside from these conditions, infantile arteriosclerosis has been observed in an increasing number of cases in which no obvious ætiological factors are apparent, but which show considerable resemblance in their clinical manifestations and striking similarity in their pathological findings. The principal

[1] "Textbook of Pediatrics", edited by Waldo E. Nelson, 1954, Saunders, Philadelphia and London, 933.

[2] *Radiology*, August, 1956.

morphological change in the arteries in these patients is marked disorganization of the internal elastic membrane accompanied by deposition of lime salts in its proximity. Concurrently, fibroblastic proliferation of the intima takes place, which may attain such proportions that the involved vascular lumen becomes much narrowed or even obliterated. Lipoid deposits are not observed in infantile arteriosclerosis; this makes it unlikely that those factors which are operative in the development of adult atherosclerosis play a significant role in the pathogenesis. The similarity of the lesions described here to those occurring in derangements of calcium and phosphorus metabolism makes attractive an explanation for the arterial changes on a metabolic basis. So far, clinical, pathological and laboratory observations have not afforded substantiation of such a concept. Possibly metabolic changes may occur which are so subtle that they have not been recognized, since there has usually been little opportunity to evaluate these patients carefully. As histological observations indicate that the incipient changes of infantile arteriosclerosis affect the internal elastic membrane, it is conceivable that a deficiency of elastic elements may, in itself or in association with extraneous factors, lead to the foregoing arterial changes. Infantile arteriosclerosis has been proved to occur in siblings. The clinical history in several instances has shown that siblings have died under similar circumstances. This observation makes it likely that genetic factors may predispose to the development of the condition. Weens and Marin point out that in most cases the clinical symptomatology has usually not been sufficiently characteristic to permit a diagnosis of this disease entity, but radiological examination should make it possible to recognize the condition during life. In all cases of unexplained heart failure and cardiac enlargement in infancy and childhood, as well as in debilitating diseases of unknown ætiology, calcification of the arteries should be searched for by proper radiological studies.

## PSYCHIC STRAIN IN REFUGEES.

RARELY, if ever, has the world seen such mass movements of population as in the present time. This *Völkerwanderung* differs very materially from the invasions of Teutons, Huns and Moslems which put an end to Roman civilization, in that the latter were composed of voluntary fighters urged on by love of adventure and hopes of conquest and spoils. What we find today is flight from foreign government, political and economic oppression, loss of possessions, harsh regulations which divide families and general uprooting of traditional ways of life. In a few weeks Austria had to succour 150,000 fugitives who had left Hungary by crossing the frontier. About half of these used Austria as the first stage in an emigration to America, Australia and other distant lands; some planned to settle down in the country of their adoption, whilst others waited to see if matters in their own home land would improve and allow a return. The reaction of the Austrian people to this crisis has been most praiseworthy: help has been liberally offered by institutions and privately by individuals, greatly reducing anxiety and discomfort in the unhappy immigrants. This friendly approach of the Austrian people has not made them insensible to the fact that there are problems concerning these fugitives which must be faced. At first there is a euphoria, a relief following escape, but soon signs and symptoms of strain manifest themselves; the morbidity is high, so is the death rate; suicides increase in number, whilst the young display a higher incidence of criminality than that amongst the people who act as hosts.

Conditions found amongst immigrants in Australia are obviously widely different from those discernible in Austria, yet the psychohygiene of both displays identical elements, though of unequal intensity. The problems presented in the Commonwealth are more akin to those encountered in North America, where quite a literature has sprung up dealing with the immigrant question, particularly as it affects those who are not conversant with English. However, wherever it occurs, the problem is medical to a considerable degree. The *Wiener medizinische Wochenschrift* of February 2, 1957, has an article by three contributors outlining the responsibility of Austrian doctors towards the unfortunate Hungarian refugees. All the obvious disabilities of the fugitives are considered, such as anxiety and reorientation states, isolation, particularly linguistic isolation, and suspicions that they are disliked by their new neighbours. One factor is especially stressed—namely, that whilst flight is a horizontal change, a fall in social status or prestige is a vertical shift, and this can be a determining factor in begetting a feeling that the future is precarious. This element has been given prominence in American studies.[1]

It is certainly remarkable that this Austrian analysis of the psychic problems of the immigrant gives us no new component not fully described and explained in papers read at the Ninth Session of the Australasian Medical Congress (British Medical Association) held in Sydney in 1955. In THE MEDICAL JOURNAL OF AUSTRALIA of October 15, 1955, there will be found a report of the contributions given to the Section of Neurology and Psychiatry, and here may be seen, especially in the addresses of B. H. Peterson and A. T. Edwards, a full exposition of the causes and suggested treatment of the "paranoid reactions" which New Australians show. The Austrian doctors do not quote from these reports, and it is evident that their attention has not been directed towards them. The parallelism in the treatment of the theme cannot fail to arouse interest locally.

## IMMUNE MECHANISMS IN RHEUMATOID ARTHRITIS.

THAT something reacts with connective tissue to the latter's detriment is a current tenet in the still loose concepts of the connective tissue disorders. Much work has been done on sampling the sera from patients whose fixed tissues have been afflicted in the hope of finding evidence in the perfusing fluid which will be specific for the disorder. With regard to rheumatoid arthritis an interesting documentation exists of the hard and often practically unrewarding work undertaken to find such a mechanism or to provide a pathognomonic test. This has been reviewed by E. Dresner.[2] In 1929 Cecil and colleagues observed that the sera of rheumatoid arthritic patients agglutinated a specific strain of hæmolytic streptococcus in high titre. This was found not to be type specific. The agglutinins were then held to be antibodies to a non-specific hæmolytic streptococcal antigen, and their presence in rheumatoid sera was widely confirmed. Agglutinins active against strains of pneumococci and staphylococci were later also described. Widespread investigations showed that significant titres of antistreptolysin O, anti-fibrinolysin, antihyaluronidase, antihæmolysin and anti-staphylolysin were all absent in rheumatoid sera. As a result of absorption studies with streptococci, staphylococci, colloidal aluminium silicate and specific antibacterial immune sera, it was shown by Oker-Blom and colleagues that agglutinating activity is specific for neither of the above organisms and cannot be correlated with serum antibody concentrations to them. Bacterial agglutination in rheumatoid arthritis is therefore non-specific and may occur apart from bacterial antigen. Wallis showed that rheumatoid sera would agglutinate collodion particle suspension in very high dilution, a property not present in normal sera. It is generally accepted that the presence of agglutinins is related to the duration and severity of the arthritis; about two-thirds of patients have them at some time in blood and also in the synovial fluid. The streptococcal and collodion agglutination tests have now been largely abandoned because of their failure in one in three cases and because of technical difficulties involved in preparing stable and uniform test preparations.

Sheep red cell agglutination by rheumatoid sera in about one-third of cases, as against one in twenty of non-

[1] "Americans in the Making", by W. C. Smith, New York, 1939.

[2] *Post-grad. M. J.*, April, 1957.

rheumatoid subjects, was noted by Waaler in 1940. The cells were previously sensitized with a non-agglutinating amount of hæmolytic amboceptor. No agglutination occurred with unsensitized cells; so it was not due to heterophile antibody. Rose (1948) found that if the sheep cells were treated with rabbit antisheep cell amboceptor, the sensitivity was greatly increased, and a test was devised expressed as a ratio of sensitized to unsensitized titres. A positive result arbitrarily taken as a differential titre of 1:16 was present in 80% of adult rheumatoid subjects tested and in 7% of controls. Heller modified this further by removing heterophile antibody first, and claimed positive results in 90% of rheumatoid arthritis patients as against 61% by Rose's technique. Further refinements have been since suggested.

In published series in which the tests have been used, positive results have followed in between 45% and 90% of cases. Kellgren (1952) found 47% of positive results in 642 cases. Greenbury and colleagues (1956) found 90% of positive results in 294 cases, rising to 95% with radiological lesions. Coggleshell (1953), in a review of 1800 published cases, found an overall positive result of 64%. Results are much more frequently positive in unequivocal than in unselected cases, but the exclusion of doubtful cases gives a bias suggesting unmerited sensitivity of the test. It should be noted that an agglutinating system positive in 60% to 70% of rheumatoid subjects is positive in 4% of controls. When the agglutinating factor is found in the blood, it is present also in the synovial fluid.

False positive results are found most commonly in "atypical" types of rheumatoid arthritis; and in disseminated *lupus erythematosus* the positive results may be as high as for rheumatoid arthritis. Positive results are rarely obtained in ankylosing spondylitis (1·5%), juvenile rheumatoid arthritis (13·5%), osteoarthritis (3%) and psoriatic arthritis (7%), and almost never in rheumatic fever. Occasional positive results have been reported in a wide miscellany of conditions; presumably these are from the group of 4% "positive" controls.

The test is now recognized not to be of value as an index of disease activity in rheumatoid arthritis, and once the result is positive it tends to remain so despite variations in the patient's condition, or steroid therapy. Positive results in rheumatoid subjects are most likely to be found in males, in those with widespread disease of long standing, especially in the presence of subcutaneous nodules. The result of the test may become positive within a few weeks of the onset of the disease. This is not usually so until after a year. Its diagnostic value fails then in the early stages of illness, when it is most needed. The test then has a fair degree of specificity for rheumatoid arthritis and for those conditions histologically characterized by fibrinoid, except notably rheumatic fever.

In about one-third of all cases of arthritis results are negative by these tests at any one time. The presence of an agglutination inhibitor was postulated and found by Ziff and colleagues (1954) in non-rheumatoid sera. This was also discovered independently by Heller and colleagues (1954) in Cohn fraction II. Ziff found the fraction to be euglobulin. A concentrate reduced the incidence of positive results in their normal subjects from 13% to 2%. Its virtually complete removal was demonstrated by the 100% failure to inhibit agglutination in known "positive" serum by rheumatoid euglobulin fractions, whereas only 5% of control sera reacted similarly. Thus failure of the euglobulin concentrate of rheumatoid serum to inhibit agglutinations provides a more sensitive index of agglutinating activity than does the direct test for agglutination. Ziff *et alii* (1956) also found inhibitor in pooled human gamma globulin which was active *in vivo* in inhibiting the agglutination reaction and caused inhibition to reappear in rheumatoid sera.

It seems that in both the sensitized sheep cell and streptococcal agglutination tests the cells and organisms have no immunological function, but serve as inert carriers of a globulin constituent of serum—in the case of the sheep cells of a gamma globulin in the amboceptor, and of the streptococci possibly a beta globulin, certainly a water-soluble one. Gamma globulin in excess can inhibit agglutination or reduce the titre of a "positive" serum, presumably by competition with the rheumatoid factor for the globulin reactant on the carrier. This reactant or "antigen" is therefore a constituent of normal human gamma globulin and also of the antisera to a wide range of antigenic stimulants. The agglutinating factor ("antibody") has been variously located in beta and gamma compartments. The evidence that these constituents can react in some sort of auto-immune way is at present slight.

Almost thirty years of labour have been involved in reaching this inconclusive state. This is not to deride its undertaking, but merely to quell the glibness which is sometimes encountered in thoughts expressed about immune mechanisms in rheumatoid arthritis. It often happens that scientific work in progress is a galaxy of apparently unrelated facts about nothing in particular, until some further grouping of known *plus* new facts reveals a simple easily followed line through the lot. Perhaps this is not so distant in regard to rheumatoid arthritis.

## SCIENCE AND WILD BERRIES.

IN this year particularly, the name William Harvey will be applied without question to the great doctor who died three centuries ago, and whom the whole of the medical world has been commemorating. However, there is another William Harvey in the picture, classed as a "miscellaneous writer and compiler". He it was who coined the aphorism "Civilization is simply a series of victories over nature", and we are reminded of this by a quaint illustration of the principle involved. A. Ravina[1] has commented on recent legislation in Germany to control the marketing of wild berries, which is apparently regarded in that country as a serious matter. For some years the problem has been under consideration, and recently the Government at Bonn has brought in regulations "to ensure to the industry and to the consumers a high quality in the berries that grow and are picked in certain regions of Germany". The berries involved include raspberries, whortleberries, red bilberries and blackberries. In these regulations the various berries are divided into commercial categories and made subject to precise specifications. For example, bilberries cannot be sold for eating purposes unless they are practically free from leaves and ripe; the same applies to red bilberries, except that they must also be quite firm; raspberries and blackberries may not be sold unless they are of uniform ripeness and are almost entirely free from calices, debris and blemishes. However, macroscopic examination is not sufficient to ensure that all these requirements shall be fulfilled, since cheating is easy. Raspberries in particular can take up a large amount of water in such a way that the fact is not apparent to the naked eye, nor can it easily be detected. Hitherto, dishonest gatherers and purveyors have been able to introduce as much as 40% of water into raspberries without detection. All this is changed now, thanks to the march of science. All that is required is the portable sugar refractometer invented by Carl Zeiss, which may be taken to the scene of the gathering, or used to test the fruit when it is offered for sale. The instrument is easily used, and the authorities controlling the sale of foodstuffs have organized short courses for its personnel (it is not necessary to be an approved chemist), which take place yearly. Ravina remarks that recent communications refer to the "psychological shock" occasioned amongst gatherers and sellers of the berries by this unforeseen development. It appears that they did not in the least expect their rustic industry to be brought under scientific control, and that all cheating has ceased. Possibly the very severe penalties threatened have had something to do with this. It seems that all this, which on the face of it strikes us as comparable to taking an axe to cut a pound of butter, is not so childish in Germany, where in certain areas berry-selling is quite a flourishing industry. We cannot, however, quite free ourselves from a certain astonishment at the manifold uses of science.

[1] *Presse méd.*, April 6, 1957.

# Abstracts from Medical Literature.

## PHYSIOLOGY.

### Source of Resting Total Mixed Saliva of Man.

L. H. SCHNEYER (*J. Appl. Physiol.*, July, 1956) has investigated the secretory activity of the small mucosal salivary glands, and the stimulatory effects of saliva collection methods, as possible causes of an initially reported discrepancy between observed values for the minute volume of resting total saliva and values calculated from flow rates of component secretions from the major glands. It has been found that the indicated discrepancy is not due to secretory activity of the mucosal glands, but is attributable to undue stimulation by the method selected initially for the collection of the total mixed saliva. Observations of the rate of flow of the total mixed saliva and of the secretions of the individual major gland pairs, under conditions which permit elimination of undue stimulation, indicate that the secretions derived from the three major salivary gland pairs fully account for the volume flow of the resting total mixed saliva.

### Electrical Activity in Chick Amnion.

C. L. PROSSER AND N. S. RAFFERTY (*Am. J. Physiol.*, December, 1956) report that isolated amnions from chick embryos showed spontaneous electrical activity, both local and conducted. Responses to barium and to shocks were conducted at an average of 2·9 centimetres per second (38° to 40°C.). Conducted responses were observed in amnions at five to ten days of incubation. Failure of conduction in older amnions appears related to the shortening and increased randomness of the muscle fibres. This preparation gives conclusive proof of conduction in nerve-free smooth muscle.

### Effect of Antrum Exclusion on Gastric Secretion.

W. R. WADDELL (*J. Appl. Physiol.*, September, 1956) has performed acid secretory tests on patients before and after vagotomy and antrum exclusion operations for duodenal ulcer. Comparison of the effect of this operation with the effect of vagotomy and gastroenterostomy has allowed evaluation of the function of the intrinsic innervation of the stomach upon acid secretion. Transection of the stomach caused decrease in acid output during basal periods and after stimulation with histamine and insulin. It is concluded that this results from interruption of intrinsic post-ganglionic parasympathetic innervation, which normally passes from the antrum to the parietal cell area in the gastric wall.

### Sleep and Variations in Certain Functional Activities.

C. McC. BROOKS, B. F. HOFFMAN, E. E. SUCKLING, F. KLEYNTJENS, E. H. KOENIG, K. S. COLEMAN AND H. J. TREUMANN (*J. Appl. Physiol.*, July, 1956) have employed multiple recording to identify and quantitate sleep and to detect functional changes associated with variations in sleep of men and women. Long periods of uninterrupted deep sleep occurred most frequently early in the night. However, the average estimated depth of sleep was similar during the first and second halves of the night. Intervals of lessened sleep were often associated with cardiac acceleration, greater variation in cycle length and body movements; but average depth of sleep did not correlate with average heart rate or number and duration of movements. Persons who slept most deeply moved less often, wakened less frequently, and showed less variation from night to night (five of six subjects). Variation in toe temperature and in frequency of sleep cycles and numerous other changes recorded did not correlate well with depth of sleep estimated from electroencephalographic records. These findings suggest that changes in heart rate or toe temperature from a basal value rather than average nightly values can be used as indicators of the depth of sleep to support interpretation of electroencephalographic tracings. Although movement most often is associated with brief alterations in the depth of sleep and in the heart rate, fewer or more moves do not necessarily result in better or poorer sleep and relaxation.

### Use of Electrical Currents to Delay Intravascular Thrombosis.

P. N. SAWYER AND B. DEUTSCH (*Am. J. Physiol.*, December, 1956) discuss previous studies on the relationship of electric phenomena to intravascular thrombosis. On the basis of these studies, experiments on dogs were designed to determine whether or not a negatively charged electrode could, by means of its orientated current, prevent formation of a thrombus in an injured vessel. With the use of electrodes of several types, a series of controlled experiments were performed which demonstrated that a current created by the technique used would delay intravascular thrombosis for periods up to twelve hours.

### Discrimination of Calcium and Strontium by the Kidney.

N. S. MACDONALD, P. NOYES AND P. C. LORICK (*Am. J. Physiol.*, January, 1957) have directly compared skeletal retention and excretion of strontium with those of calcium, by injecting solutions containing both radioisotopes, $Ca^{45}$ and $Sr^{90}$, into rats and rabbits. In normal animals, a greater fraction of the injected dose of $Ca^{45}$ was retained in the skeleton than was observed for $Sr^{90}$. In complementary fashion, the fraction of the injected $Sr^{90}$ which appeared in the urine was greater than the fraction of the dose of $Ca^{45}$ which was excreted. However, in rats in which tibial fractures were being actively calcified, this difference disappeared. The enhanced accumulation of radioactivity in deposits of new bone possessed the same ratio of $Sr^{90}$ to $Ca^{45}$ as the solution injected. Furthermore, when the functions of the kidneys of normal rabbits were impaired by poisoning with mercuric chloride or were completely extinguished by nephrectomy, again the usual differences in $Ca^{45}$ and $Sr^{90}$ deposition in bone tissue disappeared. When plasma containing both $Ca^{45}$ and $Sr^{90}$ was shaken with powdered bone, both radioisotopes were extracted in equivalent amounts. It was concluded that the avidity of bone tissue *per se* for strontium ions is not discernibly different from that for calcium ions. The retention by the skeleton of a larger fraction of an injected quantity of calcium than of simultaneously administered strontium was attributed, in part, to a renal discrimination causing a greater relative loss of strontium to the urine.

### Oxygen Requirements in Underwater Swimming.

L. G. GOFF, R. FRASSETTO AND H. SPECHT (*J. Appl. Physiol.*, September, 1956) give oxygen consumption and swimming rates for 200 open-water swims of varying distance. The average oxygen consumption varied from 1·3 to 1·9 litres per minute at average swimming rates from 0·7 to 0·9 mile per hour. A wide variation in oxygen consumption was observed under these field conditions. The range was not narrowed when the result was converted to litres of oxygen per square metre of body surface, and may result primarily from differences in individual swimming ability. Frequent subjective symptoms of carbon dioxide accumulation in the breathing equipment were reported.

### Electroretinogram in Man During Blackout.

D. H. LEWIS AND T. D. DUANE (*J. Appl. Physiol.*, July, 1956) have recorded electroretinograms from five subjects on the human centrifuge under varying degrees of accelerative stress up to and including blackout and unconsciousness. These findings were correlated with changes in the retinal circulation and with the consensual light reflex. It was found that the electroretinogram could not be employed as an objective measurement of blackout, since it persisted throughout all the experiments, as did the consensual light reflex. These findings indicate a likely origin of blackout in or near the ganglion cell layer of the retina.

## BIOCHEMISTRY.

### Hyaluronic Acid.

H. F. DEUTSCH (*J. Biol. Chem.*, January, 1957) has isolated from two human sera a very asymmetric carbohydrate-rich substance having a molecular weight near 58,000. In terms of its glucosamine content, destruction by testicular hyaluronidase and physical properties, the material appears to be hyaluronic acid.

### Vitamin D.

H. F. DE LUCA *et alii* (*J. Biol. Chem.*, January, 1957) have shown that addition of vitamin *D* to a non-rhachitogenic diet as well as to a rhachitogenic diet diminished the oxidation of citrate and reduced the resulting accumulation of α-keto-glutarate by rat kidney homogenates. By way of contrast, vitamin *D* had little or no effect on the oxidation of certain intermediates of the citric acid

cycle—*viz.*, α-keto-glutarate, succinate, fumarate and pyruvate—and likewise had little effect on the amount of citrate accumulated during these oxidations. However, it reduced the oxidation of pyruvate in the presence of oxalacetate, but increased the resulting accumulation of citrate. This is consistent with the finding that vitamin *D* decreased the conversion of citrate to α-keto-glutarate. With liver homogenates, no consistent effect of dietary additions of vitamin *D* on the oxidation either of citrate or of pyruvate *plus* oxalacetate was obtained. This is in agreement with a previous failure to demonstrate an increase in liver citrate. Although small amounts of calcium added *in vitro* were found to inhibit citrate oxidation, the effect of the vitamin could not be accounted for by the observed increase in kidney calcium.

### Thyroxine.

K. TOMITA *et alii* (*J. Biol. Chem.*, January, 1957) have studied the metabolism of thyroxine. The deiodination of thyroxine to triiodothyronine, which occurs in kidney slices, does not occur in homogenates of kidney or in particulate fractions of the homogenate. The mitochondrial fraction of rat kidney converts thyroxine and triiodothyronine to derivatives which retain the original iodine of their respective precursors. The enzymes which form the derivatives are rendered soluble by sonic oscillation of mitochondria in sucrose. DPN enhances the activity of the dialysed enzyme preparation. The enzymatic conversion products have been identified as tetraiodothyro-acetic acid and triiodothyroacetic acid by paper chromatography, by colour tests and by co-crystallization with compounds of known structure.

### Thyroxine.

E. C. WOLFF AND E. J. BALL (*J. Biol. Chem.*, February, 1957) report that the addition of thyroxine to fresh rat heart homogenates in which succinate oxidation is proceeding produces a marked increase in total oxygen consumption. It is found that this effect of thyroxine is due to its ability to prevent formation of oxalacetate, a potent inhibitor of succinate dehydrogenase. Measurement of the total α-keto acid formation during succinate oxidation in such homogenates shows that it is markedly depressed in the presence of thyroxine. The amount of α-keto acid formation varies inversely with the increase in oxygen uptake as the thyroxine concentration is altered. Identification of oxalacetate was accomplished by converting it to aspartic acid by transamination with glutamate and detection by paper chromatography. Indeed, the addition of small amounts of glutamate to fresh rat heart homogenates is found to mimic the effect of thyroxine in increasing the oxygen consumed during succinate oxidation. However, glutamate is unlike thyroxine, in that the latter is fully effective only when added initially. That thyroxine prevents oxalacetate accumulation rather than accelerating its removal, as is the case with glutamate, is further shown by the fact that DL-thyroxine in concentrations as low as $1 \cdot 5 \times 10^{-6}$M produces an inhibition of malate oxidation in homogenates. No effect of thyroxine on the conversion of fumarate to malate could be detected. Evidence is presented that the inhibitory action of thyroxine is a competitive one with DPN for malate dehydrogenase. Preliminary results indicate that other DPN-linked dehydrogenases are also inhibited by thyroxine. The possibility that this action of thyroxine is due to its interaction with the zinc component of such dehydrogenases is discussed in the light of known interactions of thyroxine with metals.

### Pyridoxine.

K. GUGGENHEIM AND E. J. DIAMANT (*J. Biol. Chem.*, February, 1957) have shown that an increased urinary excretion of xanthurenic acid and a decreased excretion of N-methylnicotanamide after the feeding of tryptophane are early signs of deprivation of pyridoxine in young rats, whereas the appearance of a typical dermatitis, accompanied by weight loss and a delayed diuretic response to water load, is a characteristic sign of severe deficiency. Deficient rats had enlarged adrenals with normal cholesterol content. The adrenals of pair-fed controls were of normal size, but contained more cholesterol than those of controls fed *ad libitum*. Cortisone treatment increased the cholesterol content of the adrenals in all the groups studied. Pair-fed control rats had a high blood glucose and liver glycogen content and showed an increased gluconeogenesis by liver slices in the presence of pyruvate. These findings, together with an elevated adrenal cholesterol level, may be considered as evidence for adrenal hyperactivity resulting from the increasing stress of prolonged food restriction. Deficient animals, although showing an increased glucose utilization by muscle, exhibited no deviation from normal carbohydrate metabolism attributable to adrenal insufficiency.

### Pasteur Effect.

V. R. POTTER *et alii* (*J. Biol. Chem.*, February, 1957) have set up a Pasteur effect in a particulate system by means of the addition of increasing quantities of rat liver mitochondria to a glycolytic system (the high-speed supernatant fraction of rat brain or tumour tissue). The mitochondria inhibit both lactate accumulation and glucose disappearance. The oxidative mechanism of the mitochondria, including the cytochrome chain and cytochrome reductase, was shown to be involved in the inhibition of glycolysis. The mitochondrial inhibition is mediated primarily by inhibition of formation of reduced DPN rather than by inhibition of formation of pyruvate. Studies on the levels of adenine nucleotides in the inhibited and uninhibited systems and studies on the effect of ADP addition have failed to support a mechanism for the mitochondrial Pasteur effect involving competition for extra mitochondrial phosphate acceptor (ADP and AMP). Studies of both the incorporation of acetate-1-$C^{14}$ and pyruvate-2-$C^{14}$ into glucose and of the dilution of glucose-2-$C^{14}$ by pools of unlabelled glycolytic intermediates provided no evidence for resynthesis of glucose by mitochondria. In view of analytical data on the level of fructose phosphates and of studies on the effect of hexose phosphate addition, it was concluded that the most likely mechanism of the Pasteur effect under the experimental conditions studied was the inhibition of the phosphohexokinase reaction and possibly also the hexokinase reaction by the oxidative system of the mitochondria.

### Urea.

G. BEATON (*Arch. Biochem.*, March, 1957) has shown that pregnant rats exhibit a smaller elevation of blood urea level following the intraperitoneal injection of either alanine or casein hydrolysate than do normal controls. This is interpreted as further evidence of a decrease in urea formation in pregnancy. The pregnant rats showed a greater and more prolonged elevation of blood urea level after the administration of urea than did non-pregnant controls; this could explain the lack of a decrease in the fasting blood urea content during gestation in the rat. Data obtained from pregnant rats after surgical removal of the fœtuses suggest that the low blood amino nitrogen content during pregnancy is due to a withdrawal of amino acids into the fœtal circulation.

### Tumours.

J. S. WOOD *et alii* (*Cancer Res.*, December, 1956) have made quantitative assays of the liver tryptophane peroxidase activity in 38 controls and 48 mice bearing subcutaneous implants of the Lewis sarcoma 241. A depression of the enzymatic activity to one-half the control level was found in mice bearing tumours less than 4·5 millilitres in volume, and during the initial eighteen-day period of tumour growth. Mice with tumours of a size larger than 4·5 millilitres or after the first eighteen days of tumour growth showed significant increases in the enzyme activity over the controls. Changes analogous to this biphasic depression and elevation of the enzyme level in tumour-bearing animals could be produced in control mice by growth hormone and by adrenal-stimulating stress respectively.

### Toxins.

J. MAGER AND E. THEODOR (*Arch. Biochem.*, March, 1957) report that somatic antigen preparations from *Salmonella paradysenteriæ* type III were found to inhibit oxygen consumption in rat or mouse liver mitochondria. The inhibitory effect was traced to a naturally-occurring (native) heptene polysaccharide contaminating these preparations. Under the standard test conditions, the hapten inhibited preferentially the oxidation of substrates the dehydrogenases of which are linked to pyridine nucleotides; the succinic oxidase showed a much lower degree of inhibition. The antigenic lipo-polysaccharide-protein complex ("complete somatic antigen") in a highly purified state did not affect the mitochondrial respiration, while polysaccharide haptens obtained by chemical degradation of the antigenic complex exhibited the inhibition pattern characteristic for the native hapten. Both the native hapten and its artificial congeners uncoupled oxidative phosphorylation in rat liver mitochondria.

# Clinico-Pathological Conferences.

## A CONFERENCE AT SYDNEY HOSPITAL.

A CLINICO-PATHOLOGICAL CONFERENCE was held at Sydney Hospital on Tuesday, August 21, 1956, DR. N. ROSS, the Medical Superintendent, in the chair. The prinicpal speaker was DR. H. M. LANDECKER.

### Clinical History.

The following clinical history was presented.

The patient was an accountant, aged thirty-one years, who was born near Sydney and had spent all his life in the city, except for a period in 1944 in North Queensland and New Guinea, where he contracted proven benign tertian malaria; for this he had been treated in hospital on five occasions. He was a married man with two children, and he did woodwork as a hobby and had had no contact with dust, chemicals or animals. He was known to have had normal X-ray appearances in his chest in 1946.

His illness, which had commenced nineteen months before his death in 1956, was characterized by progressive dyspnœa. At the onset he complained of cough with sputum and dyspnœa and was admitted to a suburban hospital, where a diagnosis of virus pneumonia was made on the basis of the investigations set out in detail in Table I. His temperature was normal except for readings of 99·6° and 99·8° F. on the fourth and fifth days; the pulse rate varied from 84 to 94 per minute. After two weeks he appeared to improve a little and was allowed to go home. However, he continued to suffer from dysphœa, and a month later was admitted to another hospital for three weeks, during which time he was afebrile. The report on a bronchoscopic examination was as follows: "A little excess of whitish secretion in the basal bronchi on the left side. Specimens of bronchial secretions were sent to Pathology." A diagnosis of tuberculosis was made.

He then resumed part-time work, but had to give it up because of increasing dyspnœa. During the next six months he was afebrile and had slight cyanosis, no finger clubbing and very little cough or sputum. There were no abnormal symptoms or signs referable to other systems. Assessment one year after the onset again revealed dyspnœa as the main and practically the only symptom. The chest was flattened, the respiratory movements were diminished, and the cardiac pulmonary second sound was accentuated. Since tubercle bacilli had never been demonstrated, a diagnosis of sarcoid was made and the patient was given calciferol. He appeared to improve and resumed work, but again was unable to continue because of dyspnœa.

He was admitted to a third hospital twelve days before his death. He said that a week previously the dyspnœa had suddenly became worse, and was accompanied by pain in the right side of his chest. He still had very little cough or sputum. There had been a gradual weight loss of seven pounds. Examination of the patient revealed some increase in the mild cyanosis, tachycardia (100 to 120 per minute) and a blood pressure of 120 millimetres of mercury, systolic, and 80 millimetres, diastolic; a pneumothorax in the right side was found on fluoroscopic examination. Manometric pressures varied from −30 to −6 millimetres of water in the pleural space. Cortisone therapy was commenced four days before the patient's death.

There was no relevant finding in the family history. A Mantoux test and a chest X-ray examination of the wife and children gave negative results.

### Clinical Discussion.

DR. N. ROSS: We have for discussion this afternoon an unusual case and we have present a number of physicians not associated with this hospital. This is quite refreshing to us. The patient died in the anti-tuberculosis hospital at Crown Street, and owing to the enthusiasm of Dr. Landecker a post-mortem examination was done at Sydney Hospital and witnessed by Dr. Landecker, who is physician to the anti-tuberculosis clinic, and who has kindly consented to discuss this case tonight. I will call on Dr. Landecker.

DR. H. M. LANDECKER: This patient, man of about thirty years, consulted me on August 4, 1954, and gave the following history. About twelve months before this consultation he was admitted to one hospital where he was treated for about three or four weeks with penicillin, "Aureomycin" and streptomycin. He left hospital very little improved and stayed at home for another month, still complaining of the same symptoms. These were cough, dyspnœa, slight expectoration and general fatigue. On questioning, I found that he had had a cough since 1945. He did not attach any importance to this, but I have been able to confirm this fact in the records at another hospital. The doctor who attended him called in a chest physician, and he was admitted to a second hospital, where more or less the same findings were recorded. At the first hospital the sputum was examined for acid-fast bacilli and for fungi, and the results were negative. In the second hospital a positive Mantoux (1/1000) was found, and very numerous specimens of sputum and bronchial washings were cultured for acid-fast bacilli with negative results.

On examination in August, 1954, I found a man looking older than his age, with a flat chest and restricted respiratory movements. The systolic blood pressure was 140 millimetres of mercury and the diastolic pressure was 80, and the second pulmonary sound was accentuated, in that it equalled in intensity the second aortic sound. The liver was firm and palpable. The spleen was not palpable. He had no peripheral lymph node enlargement. Slight cyanosis of the lips was present. I can supplement the history in stating that he had two children, aged three and five years, and the Mantoux tests and chest rays of them as well as those of his wife were negative.

At this time investigations showed urine clear; erythrocyte sedimentation rate eight millimetres (first hour), 20 millimetres second hour (Westergren); smear and culture of sputum for acid-fast bacilli, negative; blood count normal; total serum proteins as stated in notes. An X-ray examination of the chest and fluoroscopy revealed slight shift of the mediastinum to the left, and fine reticulation and nodulation of the lungs were seen. The hilar lymph nodes were not prominent, and the respiratory movements of the diaphragm were not very extensive.

When repeated, the Mantoux response (1/10,000) was negative, but a second test (1/1000) produced a positive reaction (three centimetres). Numerous specimens of sputum and gastric lavage were negative for acid-fast bacilli on smear and culture. No fungi were found in the sputum on smear or culture. When these findings became available, the diagnosis of sarcoidosis was made, and he was given calciferol (50,000 units daily) by mouth—a dosage that has been recommended by several workers.

He returned four months later, stating that he had improved; he resumed his work as an accountant. An X-ray film, however, taken at this time, showed no change.

The next time that he consulted me was in March, 1956. He said that he had worked until December, 1955, but that the dyspnœa had become worse. The cough was slightly more productive and there had been a weight loss of seven pounds.

On examination, there was tachycardia (120 per minute), the liver was unchanged; there was slight increased cyanosis; the venous pressure was normal as before. However, clinical examination revealed and fluoroscopy confirmed a right-sided pneumothorax, and on questioning he stated that ten days previously there had been a sudden increase in dyspnœa accompanied by right-sided chest pain. The dyspnœa increased and he was admitted to the chest clinic. The temperature, 99° F. on his admission, varied to a maximum of 100·4° F. In order to exclude pressure pneumothorax I inserted a needle into the right pleural space and recorded a reading of −30, −6 millimetres. A tension pneumothorax had been considered a possibility before, but on these findings it could be excluded, and, indeed, it became reasonable to postulate either atelectasis or considerable elastic recoil of the lung.

The X-ray films showed increased density of the nodulation in the lungs and a right pneumothorax. Investigations at the chest clinic showed negative results for acid-fast bacilli in his sputum. The serum proteins were 7·8 grammes *per centum*, and on electrophoresis an increase in $\gamma$ 2 and 3 globulins and in $\alpha$ 2 globulin was found. The zinc sulphate and thymol turbidity tests were as shown in the notes. There also are details of the blood count, which was essentially normal.

These details are those of my own observations, and I have been able to supplement them by X-ray pictures taken at both hospitals and by some details of those admissions that have been made available to me. These can be summarized as follows: The X-ray films show an increasing diffuse nodulation of the lungs, and show progressively increasing changes since 1953. At the second hospital a diagnosis of pulmonary tuberculosis made in 1953 was made

TABLE I.

| Investigation, Diagnosis and Treatment. | Period and Result. | | | | |
|---|---|---|---|---|---|
| | First Month. | Third Month. | Fifth Month. | One Year. | Eighteen Months |
| X-ray examination | "Scattered mottling" which after two weeks "cleared considerably". | Irregular nodulation throughout the whole of both lungs. Heart displaced to left. Lower lobe may be partially collapsed. Provisional diagnosis: (i) tuberculosis; (ii) cystic disease or congenital bronchiectasis; (iii) pneumonokoniosis (coal dust). | Pulmonary nodulation indistinguishable from tuberculosis. | Pronounced nodulation throughout both lung fields with translucency in the left apex, suggesting a bulla. | Nodular infiltration in the right pneumothorax. Increased lung markings in the middle lobe. |
| Sputum examination: | | | | | |
| Smear (acid-fast bacilli) | None found (3 specimens). | None found. | None found (including bronchoscopic specimen). | None found (numerous specimens). | None found (numerous specimens). |
| Culture (*Mycobacterium tuberculosis*). | —— | —— | Negative result (4 bronchoscopic specimens). | Negative result. | Negative result (4 specimens). |
| Culture (general) | No pathogens (2 specimens). | Negative result. | Negative result (including bronchoscopic specimen). | —— | —— |
| Culture (fungus) | Negative finding (2 specimens). | —— | —— | —— | —— |
| Gastric culture (*M. tuberculosis*) | —— | Negative result (3 specimens). | —— | Negative result. | Negative result. |
| Mantoux test | —— | Faintly positive result. | Positive result with 1:1000 old tuberculin (reaction 10 millimetres in diameter). | Negative result with 1:10,000 old tuberculin. Positive result with 1:1000 dilution (3 millimetres). | —— —— |
| Blood examination: | | | | | |
| Haemoglobin value | 16·3 grammes *per centum*. | 15·0 grammes *per centum*. | 15·0 grammes *per centum*. | 15·1 grammes *per centum*. | —— |
| White cell count | 12,000 per cubic millimetre (78% neutrophile cells, 12% lymphocytes, 3% eosinophile cells, 5% monocytes). | 11,000 per cubic millimetre (68% neutrophile cells, 23% lymphocytes, 2% eosinophile cells, 2% monocytes). | 10,400 per cubic millimetre (70% neutrophile cells, 1% eosinophile cells). | 8,300 per cubic millimetre (27% neutrophile cells, 24% lymphocytes, 2% eosinophile cells, 2% monocytes). | —— |
| Red and white cells | Normal. | Normal. | Normal. | Normal. | —— |
| Erythrocyte sedimentation rate (Westergren). | —— | —— | 20 millimetres in one hour. | 8·20 millimetres in one hour. | —— |
| Serum protein content | —— | 7·3 grammes *per centum*. | —— | 8·2 grammes *per centum* (albumin 5·0, globulin 3·2). | 7·8 grammes *per centum*. |
| Other tests | Cold agglutinins, normal result. | —— | —— | Zinc sulphate turbidity, 5·6 units. Thymol turbidity, 6·2 units. | Electrophoretogram: α-albumin 4·2, β-globulin, 0·3, γ-globulin, 1·4, globulin 1·6. Electrocardiogram: first sign of right axis deviation. No evidence of myocardial damage. |
| Diagnosis | Virus pneumonia. | Tuberculosis. | —— | Sarcoid. | —— |
| Treatment | Penicillin, streptomycin, "Aureomycin". | Streptomycin. | Streptomycin. | Calciferol. | —— |

apparently on the basis of these radiological changes as well as a positive Mantoux response. At this hospital, too, bronchoscopy was negative.

Owing to the nature of the case I inquired at length into his occupational history, and I am confident that he had not been exposed to any occupational hazard. He neither worked in nor lived close to beryllium works. His hobbies were only woodwork and gardening. He was born in a Sydney suburb and had never lived in the country. There is one other striking feature of this case. In March, 1956, when his dyspnœa was severe and cyanosis obvious, the electrocardiogram showed only the slightest evidence of right axis deviation, but no evidence of myocardial damage.

In considering the diagnosis I was naturally thinking in terms of sarcoidosis as an entity—and I need not go into that now—or as a type of reaction to an infection of which we were unable to discover the agent. All our results in this direction were entirely negative, and therefore one can only state that in my opinion this patient was suffering from sarcoidosis or a reaction similar to sarcoidosis produced by an unidentified infective agent.

What this infective agent might be I cannot say. It may have possibly been a fungus. If it were so, and since the picture does not resemble that of torulosis or aspergillosis, it would seem more likely to belong to the histoplasma or toxoplasma group, but I am unable, of course, to be certain.

DR. ROSE: We have to thank Dr. Landecker for a detailed discussion of the clinical course of this patient. He has diligently gathered many of the details to give us this comprehensive picture. Now we have present this evening Dr. Cotter Harvey, who was called into consultation at an early stage of the patient's illness. He did not know then that the patient was to die. This information is, of course, very valuable for a retrospective diagnosis. We would like Dr. Cotter Harvey to tell us what his impressions were when he saw the patient, and in the light of subsequent events to tell us what his opinion is about this case.

DR. COTTER HARVEY: Thank you, Dr. Rose, for giving me the opportunity to see the end result of a patient whom I saw only once. When I saw him in August, 1953, he gave a story of having had a cough since the war, when he had an infected antrum. Since the war he had been suffering increasing shortness of breath. He told me that he had been in bed for five weeks with a heavy cold. The earlier X-ray films shown by Dr. Landecker were taken at that time. I thought that he showed slight clubbing; also his heart was

displaced somewhat to the left and he had an accentuated pulmonary second sound. My notes commented on the X-ray appearances as follows: "There is a fine bilateral infiltration—a diffuse form of pulmonary fibrosis." I referred him for investigation to the repatriation hospital, since the symptoms dated from his war service. I thought at that time his condition was serious and significant. In writing to his doctor who referred him, I mentioned my findings as above, the possibility of bronchiectasis and of investigations including bronchoscopy and bronchograms. I mentioned that his prognosis did not appear very good, and I thought that this young man did not have a very long expectation of life. The unusual picture prompted a passing thought as to the possibility of the rare disease hæmosiderosis, although there was no evidence of mitral stenosis.

At that time the diagnosis of pulmonary tuberculosis was not in my mind—it did not seem to fit the picture, although the job of the clinicians was to exclude that. The diagnosis of sarcoidosis I thought did not fit the length of this history, which was a continuous one. Now this discrete, fine, symmetrical pulmonary fibrosis—give it any name you like—offers about 150 differential diagnoses, which include bacterial and fungal infections and dust, and all sorts of rarities. I suppose only about half a dozen of them are in the bounds of possibility here. In an older man and with a short history you would think of carcinomatosis with miliary lymphangitic spread. But the disease which I felt it might be found to be is the so-called idiopathic pulmonary fibrosis first described by Hamman and Rich, which they called acute, but which modern literature suggests may often be more chronic than they thought and may be a slowly evolving process—a slow strangling of the alveoli by increased fibroblastic reaction. The cause is quite unknown and that might be what was happening. The picture was fine reticular nodulation as Dr. Landecker says, going on towards the end to a somewhat honeycomb appearance. His dyspnœa was, I take it, extreme towards the end, and he died as it were of asphyxia. This is the sort of way in which they do go. Physiological studies would have been interesting during the course of the illness to see what was going on. These studies are of some value to tell us with some degree of accuracy at what level the lesion appears to be. They are quite different in sarcoidosis from those of interstitial pulmonary fibrosis. I could not deny the possibility of sarcoidosis, which is always turning up in most obscure ways; I simply say this—in the majority of sarcoids as I see them dyspnœa is not an outstanding symptom despite remarkable X-ray pictures. They are picked up, as Dr. Landecker knows better than I do, on mass X-ray surveys without symptoms and often have a picture just like this, and yet for physiological reasons which I will not go into they do not have interference in the alveoli, they are not short of breath.

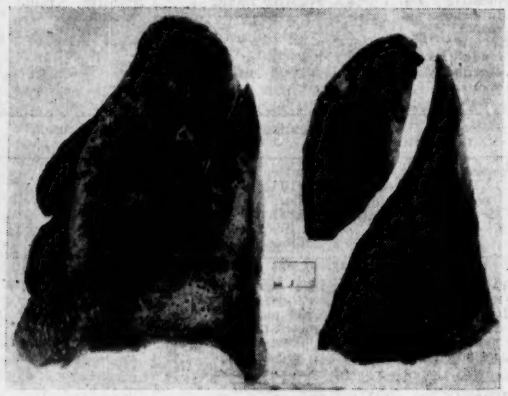

FIGURE I.

Photographs of the lungs. The cut surfaces show diffuse fibrosis, most severe in patches beneath the pleura, and some regions with a honeycomb appearance. The pleural surfaces have a cobble-stone appearance.

The long-standing story does not seem to fit, although sarcoid can do that sort of thing—that is, slowly evolve with fibrosis supervening on the sarcoid condition. The occurrence of preterminal pneumothorax was just an emphysematous bulla bursting into the pleural space in a patient whose fibrosis was extreme; it undoubtedly aggravated and precipitated his end. But I do not think there is any infectious element about that. I feel that this is the sort of thing we call Hamman-Rich idiopathic interstitial pulmonary fibrosis.

DR. ROSS: Thank you, Dr. Cotter Harvey. Present here this evening we have Dr. Karen Helms, who also saw the patient during life. Would you care to comment, Dr. Helms?

DR. KAREN HELMS: I, too, only saw this patient once. He was a young man with symmetrical pulmonary opacities affecting all his lung fields, and complaining of dyspnœa. The picture makes me think immediately now of interstitial pulmonary fibrosis. The only sure way of diagnosing this condition during life is, of course, by pulmonary biopsy. I do not think that people who have not had much experience in trying to diagnose pulmonary tuberculosis realize how very difficult a problem it is. As you know, the disease is protean in its manifestations as far as the radiological picture is concerned. It is often difficult to get positive bacteriology. This disease now is too widespread to make one think first of tuberculosis, although I think in the first X-ray film we had, it might have been considered. The latest films and the history of progressive dyspnœa suggest a diagnosis of diffuse chronic interstitial fibrosis of the lungs.

DR. ROSS: Thank you, Dr. Helms. I do not know the diagnosis in this case, but I would like to say that the people who have spoken so far have not necessarily made the correct diagnosis. I do not want others in the audience to be discouraged from speaking. Are there any representatives from this hospital, who would care to comment?

DR. J. RAFTOS: I have not very much to add to the discussion of the case, but would like to point out that we have had, during the past two years, two young patients dying of asphyxiation. One was thirty-two and the other thirty-six years of age. The diagnosis in the first case was disseminated *lupus erythematosus*. The second patient died of diffuse reticulosarcoma of the lungs, and initially at any rate the X-ray picture was very similar to the picture we see in this case. At the time of her death she had no extrapulmonary manifestations, although she had had them previously. I would agree with Dr. Helms that the only way to confirm the diagnosis of diffuse pulmonary fibrosis would be by lung biopsy. After all, the surgeons when in doubt have a look, and I do not see why we should not do the same thing.

PROFESSOR W. K. INGLIS: I would like to ask Dr. Cotter Harvey a question. I understood Dr. Cotter Harvey to mention the word honeycomb lungs. Was I correct in that, Dr. Harvey? May I ask is there radiological evidence in any of the skiagrams of honeycombed lungs?

DR. COTTER HARVEY: It certainly is not as obvious as was the case recently shown at The Royal Australasian College of Physicians, in which the interstitial changes were more marked than this. I think in this region on the X-ray film in the mottled area there is this appearance. It is not really a radiological concept, and refers more to what is seen in the gross appearance of the lung at post-mortem examination than to what is seen on the X-ray picture. But this shows here an interstitial picture with highlights, probably areas of emphysema, and it represents some degree of honeycombing, although this is not quite as typical as is shown sometimes.

DR. ROSS: Does that answer your question, Dr. Inglis?

PROFESSOR INGLIS: Yes. I understand now that there is some evidence of honeycombed lungs.

DR. HARVEY: I would not press that.

DR. ROSS: We have present some members of the staff of the Kanematsu Institute. In view of the physiological problems regarding raised pulmonary function, would they care to make some comment?

DR. W. SIMMONDS: I think Dr. Cotter Harvey has hinted quite clearly what he thinks. Physiologically there appears to be a defect in the diffusion of gases from the lung alveoli to the blood in the lung. That is why he indicated that tests of lung function would be very interesting. In such cases the lung appears to function normally as a bellows as the vital capacity and the breathing capacity are normal, but the blood gases are extremely instructive—they are nearly normal at rest in the earlier stages, but with any exertion, any extra load of oxygen requirement, blood oxygen falls pretty steeply, and as the defect becomes more severe, carbon dioxide in the blood would rise.

DR. ROSS: Could you have been of any assistance to the physician, Dr. Simmons, in arriving at the diagnosis.

DR. SIMMONDS: I do not think so at all. Dr. Cotter Harvey and Dr. Landecker and the other physicians have clearly observed the vital features with their eyes. However, one could follow the progress better and perhaps prevent an acute episode of anoxic failure if one had information about the blood gases.

DR. W. EVANS: The differential diagnosis appears to me to lie largely between a malignancy, some chronic infection, or, as Dr. Raftos has suggested, diffuse *lupus erythematosus*. I must say I favour malignancy to some degree. There are some things against—the lapse of time that the patient lived after its onset is against it; but the very strong point in its favour is the fact that there was very marked enlargement of the hilar glands with pulmonary collapse. This is very suggestive of malignancy tracking up the lymph channels to the bronchial glands. So that would be in my opinion the first diagnosis. I do not think it is a diffuse *lupus erythematosus*—there was no other history of that as it was given to us; there were no signs and symptoms of that. The other point made by Dr. Cotter Harvey and Dr. Helms, the question of tuberculosis. Well, that seems unlikely in view of the many examinations that have been made for tubercle bacilli, with negative results. The possibility of sarcoidosis cannot be eliminated, but it does not seem quite to follow the history of that, and the X-ray films do not quite suggest it. Histoplasmosis also cannot be excluded and must be considered; but I favour the view that it is a diffuse reticulosarcoma or something of that type invading the lymph glands and causing pulmonary collapse.

DR. ROSE: Would any other members of the audience care to contribute to the discussion?

DR. K. B. NOAD: Mr. Chairman, could I ask, having arrived late, whether the condition of diffuse pulmonary fibrosis has been mentioned in the discussion?

DR. ROSE: That condition has been mentioned among others.

PROFESSOR INGLIS: I feel, Mr. Chairman, that I am rather out of place in this discussion, because you are dealing with the clinical aspects of the case. It so happens that some thirty years ago a case came to my notice where there was honeycomb lung, and terminal pneumothorax, and where there was diffuse involvement as well as focal involvement of the interstitial tissues, and also some affection of the lymph nodes of the hilum. Twenty years ago another case came under my notice. Honeycomb lung is what I specially asked about, because in each of those patients there was double honeycomb lung and there was spontaneous pneumothorax near the finish; in the second of those two cases the lymph nodes at the root of the lung were affected, and it was a growth—it was called reticulosarcoma at that time. The interesting feature, however, is that in both of those cases there were cells which showed a remarkable resemblance to muscle. The Scandinavians, in particular, have emphasized the fact that you may find this condition—what they call diffuse myomatosis or muscle cirrhosis—in honeycomb lungs. I have different views in regard to certain aspects of this, but I would like to put forward at this stage the possibility of the present case being in that category, because the outstanding features of dyspnœa and cyanosis, and mighty little else as far as I can see, were associated with honeycombed lung, with nodular as well as diffuse involvement of the tissues of the lung, and with involvement of the hilar and paraaortic lymph nodes. So I suggest that as a possibility.

DR. ROSE: Thank you, Dr. Inglis. I will ask Dr. Palmer to discuss the pathological findings.

### Report of Autopsy.

DR. A. A. PALMER: The patient was a man, aged thirty-five years, five feet four inches in height, and weighing eight stone three pounds. Abnormalities were found only in the lungs and pleura. There was no pleural effusion, but there was fibrinous pleurisy on the right side. The lungs were voluminous; the surface showed pinkish-grey nodules with the appearance of morocco leather or of a "hob-nailed liver". The cut surface is also unusual, the pink stain in the centre is due to incomplete fixation. An irregular zone of fibrosis was present beneath the pleural surface spreading into the lung (Figure I). This was less marked at the base, where the subpleural zone had a honeycombed appearance. In both lungs at the anterior border several of these bullæ projected, and one was presumably the source of the spontaneous pneumothorax. Each lung weighed 20 ounces—that is, 560 grammes—which is generally considered to be within normal limits. The heart weighed 11 ounces—that is, about 300 grammes—and was not notably abnormal.

Microscopically, beneath the pleural surfaces where the fibrosis is most severe there are extensive areas of fibrosis with no remaining alveoli. The cavity is visible with the naked eye in these regions, and often resembles bronchioles. Where fibrosis is less it can be seen to commence in organizing exudate. This exudate resembles fibrin, but is often in a compact layer against the alveolar wall similar to hyaline membrane. The alveolar walls are congested with conspicuous tortuous vessels, and show some infiltration with lymphocytes and fibroblasts. In the alveoli are a great variety of histiocytes, occasional foreign-body giant cells and peculiar giant cells with large nuclei and prominent nucleoli, and in some places there are sheets of proliferating epithelial cells.

The appearances we have noted form a small but recognizable disease entity described by Hamman and Rich, and known as acute diffuse pulmonary fibrosis. Interstitial pneumonias of a similar type are more common in children. A 1955 review contains a total of 25 cases reported up to that time. The clinical course varies from a few months to three years and is notable for a low-grade fever and progressive dyspnœa. *Cor pulmonale* may or may not be present. There are no figures for serum proteins to compare with those in this case. The ætiology of the condition is entirely unknown. Bacteriological investigations have rarely been made. In our case Professor N. Stanley investigated the possibility of virus by means of tissue culture, egg culture and adult and suckling mice. No significant virus was isolated, and the psittacosis group was excluded.

### Diagnosis.

Diffuse interstitial fibrosis of the lungs.

# British Medical Association.

## VICTORIAN BRANCH.

### Influenza Vaccine.

THE following letter is published at the request of the Medical Secretary of the Victorian Branch of the British Medical Association.

MINISTER OF HEALTH, VICTORIA.

295 Queen Street,
Melbourne,
27th June, 1957.

Dear Dr. McCutcheon,

Dr. Brennan[1] informs me that your Council would appreciate an authoritative statement on distribution of influenza vaccine in Victoria.

The Commonwealth Serum Laboratories, in conjunction with the Hall Institute, have added to the influenza vaccine against the common types A and B the particular type of virus responsible for the widespread epidemics occurring at present in Eastern countries.

There is reason to believe that all age groups would be susceptible to the new strain, and it is manifestly impossible to protect the entire population within the time available between now and the time when the infection is likely to be introduced.

The Commonwealth Government, realising that demand will far outstrip supply, has arranged to issue the total vaccine produced on a per capita basis to each State, hence approximately one quarter of the vaccine produced is available for the people of Victoria. At present this is in the region of 10,000 doses per week.

Since a blanket protection is impossible I have accepted the advice of the Commission of Public Health to give the first priority to medical and nursing services, not only to have staff available to nurse those who suffer from influenza infection, but also to obviate disorganization of hospital services generally.

I have also arranged for Municipal Councils to be supplied with vaccine to protect their health staff—Medical Officers, Infant Welfare Nurses, Health Inspectors, and Home Helps.

Many large undertakings, to avoid disorganization of essential services through illness of their staff, have ordered vaccine, and these orders will be fulfilled by the Commonwealth Serum Laboratories when the high priority group's needs have been satisfied.

[1] Dr. Kevin Brennan, Chief Health Officer for Victoria.

Another group who require protection are persons whose life might be endangered by an attack of influenza because of an already weakened physical condition. This group can only be selected by their attending physicians, and the material to protect these patients should be obtained by doctors from their ordinary sources of supply or directly from the Commonwealth Serum Laboratories. A rigid classification of priorities is not considered practicable.

Yours faithfully,
(Signed) E. P. CAMERON,
Minister of Health.

Dr. A. B. McCutcheon,
President,
British Medical Association,
Victorian Branch,
426 Albert Street,
East Melbourne.

## Out of the Past.

*In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.*

### THE USE OF KANGAROO TENDONS FOR LIGATURES.[1]

[From *The Australasian Medical Gazette*, March, 1884.]

IN the *New England Medical Monthly* for June, 1883, Dr. Henry O'Marey of Boston is credited with the discovery that fibres of kangaroo tendons aseptically prepared make the best ligatures and sutures for surgical purposes. We would call attention to the fact that Mr. T. M. Girdlestone F.R.C.S. Eng. of Melbourne is the surgeon who is really entitled to the credit of this discovery and that acting on his recommendations these tendons have been for some seven years frequently used by him and other surgeons in Australia and England. He first exhibited tendons, prepared by himself, at a meeting of the Medical Society of Victoria held on December 5, 1877 and called the attention of the profession to their usefulness giving his own experience of their use.

## Correspondence.

### THE L.E. CELL TEST.

SIR: We would again like to comment on the subject of systemic *lupus erythematosus* and the L.E. test, which almost filled the journal of June 29, with the interesting papers by D. C. Cowling and I. D. Thomas, and those by the late L. J. A. Parr and others.

The fact that so much space was allotted to this disease complex shows the growing awakening of its great importance in the whole field of medicine. There is not one branch of medicine in which every worker should not be acutely aware of the natural history of the disease and its incidence. Cowling and Thomas in their summary note the wide variation in their investigations from the classical picture of the disease. In our opinion, the sooner the classical picture of the disease is altered, the better will be our understanding. Our conception of the disease is that of an inborn fault in metabolism, probably present from the earliest years of life, making the sufferer subject to the most protean manifestations which may affect any tissue in the body for a period of time, and then undergoing a natural process of remission, only later to affect the same or another tissue.

We believe that the appearances of the disease after the exhibition of drugs, sera, antibiotics and injections, after surgical operations, during pregnancy and the puerperium, after infection, after exposure to sunlight, are simply a trigger mechanism of an inborn fault present long before the particular episode.

[1] From the original in the Mitchell Library, Sydney.

The paper of Moore and Lutz (*J. Chronic Dis.*, 1: 297) and our own paper (*Australian J. Dermat.*, Vol. 3, No. 4) bring out this point clearly. In our opinion it is possible that further research in this field may be the most important advance in medicine since the advent of bacteriology in bringing to light and correlating many hitherto unexplained disease processes.

Yours, etc.,
W. H. WARD,
W. W. GUNTHER,
A. H. MCGEOCH,
D. A. W. DOWNIE.

Commercial Bank Chambers,
17 Bolton Street,
Newcastle.
July 2, 1957.

## Post-Graduate Work.

### THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

#### Week-End Course in the Use of Radio-Isotopes in Medicine.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that a week-end course in the use of radioisotopes in medicine will be held at Saint Vincent's Hospital, Sydney, on Saturday, July 27, and at The Royal North Shore Hospital of Sydney on Sunday morning, July 28, 1957, under the supervision of Dr. Gordon C. Smith.

By arrangement with the New South Wales State Cancer Council, the course will be free to all medical practitioners. It has been designed to provide basic elementary data about the physics and the diagnostic and therapeutic uses of radioisotopes in medicine. The programme will be as follows:

Saturday, July 27, 1957, Students' Lecture Room, Saint Vincent's Hospital, Darlinghurst: 9.30 a.m., opening address, "Medical Application of Radio-Isotopes", Professor C. R. Bickerton Blackburn; 10 a.m., "Radio-Isotopes: Definition, Detection and Assay", Dr. E. P. George; 10.45 to 11 a.m., discussion; 11.30 a.m., "Production and Procurement of Radio-Isotopes", Mr. D. J. Stevens; 12.15 p.m., discussion; 2 p.m., "Isotope Applications in Therapy", Dr. H. J. Ham, Dr. L. Atkinson, Mr. B. W. Scott; 3 p.m., discussion; 3.30 p.m., "Investigative Use of Radiogold in Cancer of the Uterine Cervix", Dr. K. A. McGarrity, Dr. J. M. Garvan; 4.30 p.m., discussion.

Sunday, July 28, 1957, Students' Lecture Room, The Royal North Shore Hospital of Sydney: 9.15 a.m., "Use of Radio-iodine in Thyroid Disease", Dr. F. F. Rundle, Dr. T. H. Oddie; 10.15 a.m., discussion; 10.45 a.m., "Uses of Radio-Isotopes in Hæmatology", Dr. C. K. Hambly, Dr. R. J. Walsh, Dr. P. K. Lamond; 11.45 a.m., discussion; 12 noon, "Health Protection in the Use of Radio-Isotopes", Dr. G. C. Smith; 12.45 p.m., discussion.

By courtesy of the Foreign Service of the United States of America, a special photographic demonstration on the use of isotopes in the treatment of cancer will be set up.

In order that suitable catering facilities may be provided, those wishing to participate are requested to make formal application to the Course Secretary, The Post-Graduate Committee in Medicine, 131 Macquarie Street, Sydney (telephones: BU 4497-4498), from whom programmes may be obtained.

### SEMINARS AT THE ROYAL PRINCE ALFRED HOSPITAL.

THE following seminars will be held on Friday from 1.15 to 2.15 p.m. in the Scot Skirving Lecture Theatre, Royal Prince Alfred Hospital, Sydney, from July 12 to November 1, 1957. All members of the medical profession are invited to attend.

July 12, thoracic section, "Pleural, Pulmonary and Scalene Node Biopsy in the Evaluation of Intrathoracic Disease". July 19, cardio-vascular section, "Cardiac Competence". July 26, endocrinology and metabolism section, "Pregnancy in the Diabetic", Dr. G. M. Parkin. August 2, gastro-enterology section, "Diverticula in the Upper Alimentary

Tract", Dr. N. R. Wyndham. August 9, neurology section, "Encephalitis", Dr. J. L. Allsop and Dr. Phyllis Rountree. August 16, thoracic section, "The Role of Allergy in Chronic Respiratory Disease", Dr. H. M. Rennie and Dr. Peter Waugh. August 23, hæmatology section, "Recent Studies on Non-Specific Immunity", Professor Robert Cruickshank, Director of Wright-Fleming Institute, St. Mary's Hospital, London (by invitation). August 30, cardio-vascular section, "Phonocardiography". September 6, endocrinology and metabolism section, "Uræmia", Dr. W. A. Bye. September 13 and 20, no seminar. September 27, thoracic section, "Thirty-Two Years' Experience in Tuberculosis Therapy", Dr. Cotter Harvey. October 4, pædiatrics section, "Congenital Anomalies of the Gastro-Intestinal Tract", Dr. S. P. Bellmaine. (To be followed by a clinical meeting at the Royal Alexandra Hospital for Children, Camperdown, at 4 p.m.) October 11, hæmatology section, "The Use of Radioactive Isotopes in the Determination of Blood Volume", Dr. L. P. Lamond, Saint Vincent's Hospital (by invitation). October 18, no seminar. October 25, gastro-enterology section, "Mortality from Gastric Ulcer", Dr. B. P. Billington. November 1, cardio-vascular section, "Symposium on Dyspnœa".

# Congress Notes.

## AUSTRALASIAN MEDICAL CONGRESS (BRITISH MEDICAL ASSOCIATION).

THE Executive Committee of the Australasian Medical Congress (British Medical Association), Tenth Session, to be held at Hobart from March 1 to 7, 1958, has forwarded the following notes for publication.

It is now less than eight months to Congress, and preparations for it are reaching a faster *tempo*. Since only about 100 doctors are involved in the organization out of the 200 or so throughout the State, it is evident that practically all the doctors in Hobart are working on some aspect to make Congress a success.

The wool sales are being held in Hobart in the week preceding Congress, and accommodation during that week is very limited. Those attending the sales will be leaving Hobart on Friday, February 28; so members coming to Congress would be best advised to plan their visit to commence on the Friday or at the week-end.

So far, about 200 applications for membership have been received (this means 400 people), and it is reemphasized that early application is essential if reasonable accommodation is to be expected. Wrest Point Hotel is full, and the other main hotels are filling fairly rapidly. Application forms are available from the following Local State Secretaries: *New South Wales*: Dr. M. S. Alexander, O.B.E., c.o. British Medical Association (New South Wales Branch), 135 Macquarie Street, Sydney. *New Zealand*: North Island, Dr. Warwick Macky, 94 Remuera Road, Auckland; South Island, Dr. C. Gresson, 24 Weka Street, Fendalton, Christchurch. *Queensland*: Dr. W. D. Friend, 88 L'Estrange Terrace, Kelvin Grove, Brisbane. *South Australia*: Dr. Robert Hecker, 163 North Terrace, Adelaide. *Tasmania*: Dr. L. W. Knight, 169 Macquarie Street, Hobart. *Victoria*: Dr. C. H. Dickson, Medical Society Hall, 426 Albert Street, East Melbourne. *Western Australia*: Dr. J. R. H. Watson, 246 St. George's Terrace, Perth.

We have been advised by Australian National Airways that both Australian National Airways and Trans-Australian Airways have agreed that there shall be a 45-pound free baggage allowance made to delegates to the Congress. This extra allowance does not extend to delegates' wives, children or friends.

The Secretaries of the sixteen Scientific Sections were published in THE MEDICAL JOURNAL OF AUSTRALIA on March 16, 1957. One change has occurred, *viz.*, the Secretary of the Section of Anæsthesia is now Dr. Jean Oakes, 1, The Esplanade, Bellerive, Hobart, Tasmania. The Presidents of the various Sections are as follows: *Anæsthesia*: Dr. R. H. Orton, Victoria. *Dermatology*: Dr. C. F. Robinson, M.C., New South Wales. *History of Medicine*: Associate Professor K. F. Russell, Victoria. *Medicine and Experimental Medicine*: Dr. R. Whishaw, C.B.E., Tasmania. *Naval, Military and Air Force Medicine and Surgery*: Surgeon Rear-Admiral L. Lockwood, C.B.E., M.V.O., D.S.C., Victoria. *Neurology, Neurosurgery and Psychiatry*: Dr. E. G. Robertson, Victoria. *Obstetrics and Gynæcology*: Dr. R. F. Matters, V.R.D., South

## DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED JUNE 29, 1957.[1]

| Disease. | New South Wales. | Victoria. | Queensland. | South Australia. | Western Australia. | Tasmania. | Northern Territory. | Australian Capital Territory. | Australia. |
|---|---|---|---|---|---|---|---|---|---|
| Acute Rheumatism | 1 | 6(5) | 2 | .. | .. | .. | .. | .. | 9 |
| Amœbiasis | .. | .. | 2 | .. | .. | 1 | .. | .. | 3 |
| Ancylostomiasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Anthrax | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Bilharziasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Brucellosis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Cholera | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Chorea (St. Vitus) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Dengue | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Diarrhœa (Infantile) | .. | 21(16) | 2(2) | .. | .. | .. | .. | .. | 23 |
| Diphtheria | 1(1) | .. | 1 | .. | 3(3) | .. | .. | .. | 5 |
| Dysentery (Bacillary) | .. | .. | .. | 1 | .. | .. | .. | .. | 1 |
| Encephalitis | .. | 3(2) | .. | .. | .. | .. | .. | .. | 3 |
| Filariasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Homologous Serum Jaundice | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Hydatid | .. | .. | .. | .. | .. | 1(1) | .. | .. | 1 |
| Infective Hepatitis | 35(14) | 30(13) | .. | 6(6) | 9(4) | 2 | .. | .. | 82 |
| Lead Poisoning | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Leprosy | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Leptospirosis | .. | .. | 1(1) | .. | .. | .. | .. | .. | 1(1) |
| Malaria | .. | .. | 1 | .. | .. | .. | .. | .. | 1 |
| Meningococcal Infection | 3 | 2(2) | .. | .. | .. | .. | .. | .. | 5 |
| Ophthalmia | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Ornithosis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Paratyphoid | 1(1) | .. | .. | .. | .. | .. | .. | .. | 1 |
| Plague | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Poliomyelitis | 1(1) | .. | 3 | .. | .. | .. | .. | .. | 4 |
| Puerperal Fever | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Rubella | .. | 47(39) | .. | 62(21) | 2(1) | .. | .. | .. | 111 |
| Salmonella Infection | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Scarlet Fever | 11(7) | 22(12) | 1(1) | 7(2) | 4(3) | 1 | .. | .. | 46 |
| Smallpox | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Tetanus | .. | 2(2) | .. | .. | .. | .. | .. | .. | 2 |
| Trachoma | .. | .. | .. | .. | .. | .. | 1 | .. | 1 |
| Trichinosis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Tuberculosis | 36(26) | 20(17) | 13(6) | 7(5) | 18(6) | 3(2) | .. | .. | 97 |
| Typhoid Fever | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Typhus (Flea-, Mite- and Tick-borne) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Typhus (Louse-borne) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Yellow Fever | .. | .. | .. | .. | .. | .. | .. | .. | .. |

[1] Figures in parentheses are those for the metropolitan area.

Australia. *Ophthalmology*: Dr. C. G. H. Blakemore, New South Wales. *Orthopædics*: Dr. N. S. Gunning, South Australia. *Oto-Rhino-Laryngology*: Dr. Ashleigh O. Davy, M.V.O., New South Wales. *Pædiatrics*: Dr. L. H. Hughes, New South Wales. *Pathology, Bacteriology, Biochemistry and Forensic Medicine*: Professor E. S. J. King, Victoria. *Public Health, Industrial Medicine and Hospital Administration*: Professor D. Gordon, Queensland. *Radiology and Radiotherapy*: Dr. Colin Gurner, South Australia. *Rehabilitation and Physical Medicine*: Dr. R. F. May, Victoria. *Surgery*: Dr. J. Steigrad, C.B.E., E.D., New South Wales.

The Plenary Session speakers so far arranged are as follows: "Thyroid Diseases": physician, Dr. A. W. Steinbeck; public health, Dr. F. Clements; surgeon, Dr. G. R. A. Syme; radiotherapist, Dr. W. P. Holman; opener, Dr. Basil S. Hetzel. "Fluids and Electrolytes in Health and Disease": surgeon, Professor M. Ewing; physician, not yet decided. "Heart Failure": physician, Dr. J. Halliday; surgeon, Dr. I. Monk; research cardiologist, Dr. B. Sinclair-Smith; openers, Professor R. Lovell or Dr. Austin Doyle.

There will be several eminent visitors from overseas, but these arrangements are not yet complete.

A Trades Exhibition is being held in the University grounds, and for this a temporary building is being erected.

The social programme will include a garden party at Government House on the Wednesday afternoon, a subscription dinner for 400 on Thursday night, and a ball on the final night. On other nights there will be private entertainment.

Facilities are being provided for the care during the day of young children accompanying visiting members.

If you are coming to Congress, but have not yet joined, please do so now.

## Corrigendum.

DR. GODFREY HARRIS has advised us that in his letter published under the heading "William Harvey, 1578-1657" in the issue of July 6, 1957, the publication date of Cecil and Loeb's "Textbook of Medicine" was given wrongly. This should be 1955, not 1935, as Dr. Harris's letter stated.

## Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Milder, Emil, registered under Section 17 (2) (*a*) of the *Medical Practitioners Act*, 1938-1957, 57 Darlinghurst Road, Kings Cross, New South Wales.

Grady, James, M.B., B.S., 1953 (Univ. Sydney), 25 Gartfern Avenue, Five Dock, New South Wales.

The undermentioned have applied for election as members of the South Australian Branch of the British Medical Association:

Rugless, Margaret, M.B., B.S., 1947 (Univ. Sydney), Main Road, Paradise, South Australia.

Speed, Isobel Ethel, M.B., B.S., 1956 (Univ. Adelaide), 60 Devitt Avenue, Payneham South, South Australia.

Fritsch, Mary Walda, M.B., B.S., 1954 (Univ. Adelaide), 40 Grant Avenue, Rose Park, South Australia.

Halley, Peter, M.B., B.S., 1956 (Univ. Adelaide), 18 Torrens Street, Gilberton, South Australia.

Steward, Harrold Dunning, M.B., B.S., 1950 (Univ. Adelaide), 4 Fifth Avenue, Helmsdale, South Australia.

The undermentioned have been elected as members of the South Australian Branch of the British Medical Association: Thillainath, Arumugam, M.B., B.S., 1955 (Univ. Melbourne); Weston, Frank Keith, M.B., B.S., 1956 (Univ. Adelaide); Smith, Frank Stewart, M.B., B.S., 1955 (Univ. Sydney).

## Medical Appointments.

Dr. S. K. Dwyer has been appointed an official visitor to the Mental Hospital, Morisset, New South Wales.

Dr. J. F. Brennan has been appointed Medical Officer of Health, Bothwell Municipality, Tasmania.

Dr. T. H. Walker has been appointed Medical Officer of Health, Ulverstone Municipality, Tasmania.

Dr. K. D. Murray, Dr. I. J. Forbes and Dr. L. L. Wilson have been appointed honorary clinical assistants to the department of pathology, Royal Adelaide Hospital.

## Deaths.

THE following deaths have been announced:

COYLE.—Edward Frank Coyle, on June 14, 1957, at Sydney.

QUESSY.—Pierre Leon Antoine Quessy, on July 4, 1957, at Earlwood, New South Wales.

RAYMENT.—James Tareton Rayment, on July 6, 1957, at Dubbo, New South Wales.

## Diary for the Month.

JULY 23.—New South Wales Branch, B.M.A.: Ethics Committee.
JULY 24.—Victorian Branch, B.M.A.: Branch Council.
JULY 25.—New South Wales Branch, B.M.A.: Branch Meeting.
JULY 26.—Queensland Branch, B.M.A.: Council Meeting.

## Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

*New South Wales Branch* (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

*Queensland Branch* (Honorary Secretary, B.M.A. House, 88 L'Estrange Terrace, Kelvin Grove, Brisbane): Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

*South Australian Branch* (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

## Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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